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MARROW INSUFFICIENCY *

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BY reason of its wide dispersion through the body the bone marrow is not ordinarily viewed as an integral organ; yet such it is, and an extremely interesting and important one in the light of its manifold functions. Its hematopoietic activity in the formation of erythrocytes, leukocytes and thrombocytes is generally appreciated; but its wealth of reticulo-endothelium determines certain further functions that are less widely understood. Bile pigment is formed in great amounts in the marrow. Antibodies are likewise developed through reticulo-endothelial activity. However, particular attention in the present relation is directed toward the commoner cellular elements of the circulating blood which have their origin in the bone marrow.[1]

Under normal conditions the bone marrow is the sole source of the erythrocytes, polymorphonuclear leukocytes and thrombocytes in adult life. During fetal existence the liver, spleen, and lymph nodes participate in this function. Reversion to complete hematopoiesis on the part of the liver and spleen occurs only under unusual circumstances in extrauterine life. At birth, the functioning red marrow occupies the entire shafts of the long bones. By the sixteenth year, active marrow is found in the ends of the long bones, in flat bones, and in small, spongy bones. Attention on the part of students of blood dyscrasias to this normal recession of myeloid activity would eliminate much misleading detail from the literature. In general, biopsy and necropsy studies of sternal and rib marrow will afford much more accurate information of the essential disease process and myeloid state in the adult than will the marrow from the shafts of long bones.

There is no complete agreement as to the histogenesis of the mature blood cells arising in the bone marrow. The generally accepted course is represented in figure 1. The root cell, or hemoblast, is held responsible for the development of the polymorphonuclear leukocytes, erythrocytes, and platelets. Consensus of hematologists holds to the existence of special precursors in the myelocytic series for each of the granular forms of polymorphonuclear leukocytes, neutrophilic, eosinophilic and basophilic. The

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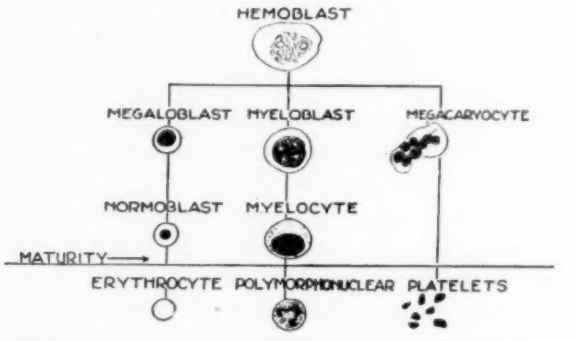
megakaryocyte of the marrow is believed to be the sole source of the thrombocyte; but under disease conditions these large cells may appear in other than myeloid tissue.[2] Authorities differ widely in their opinions as to the development of the red blood cell series. Many claim that there is no relationship between the megaloblast and the normocyte or erythrocyte. This group maintains that there exists a precursor of relatively proportional size for each mature red blood cell, macrocyte, normocyte, and microcyte. For the present purpose, at least, the question would appear highly academic.

Two mechanisms of delivery of the cellular products of marrow activity into the circulatory blood stream have been invoked, namely, ameboid movement of the involved cells and extrusion by growth pressure. Certain histologic and anatomic features of the bone marrow indicate a close relationship between structure and function. There is no true capillary network.



SCHEMATIC REPRESENTATION OF DERIVATION OF COMMON BLOOD CELLS FROM THE PRIMITIVE BONE MARROW CELL.

FIG. 1.

The arterial capillaries of the marrow are relatively long and, without side branches or anastomoses, open directly into venous sinusoids or sinuses. The lining endothelium of the latter is very tenuous. From these conditions the resultant sluggish blood flow and the thin endothelial barrier favor the ready delivery of blood cells from the marrow to the circulation. Then, too, the more or less actively proliferating marrow is encased in the inelastic bone. This inelasticity is further enhanced by the semifluid yellow marrow which fills the major portion of the long bones. This circumstance, while encouraging ameboid movement toward the venous sinuses, is especially important in giving direction to growth pressure.

The ameboid activity of the polymorphonuclear elements becomes increasingly more marked with maturity, and this mode of migration is generally accepted as operative in the delivery of this group of white blood cells from the bone marrow to the blood. The blood platelets are also known to possess ameboid movements; but apparently the factor of growth pressure is the potent one in the delivery of the erythrocytes. "The vis a tergo which

pushes the cells into the blood stream is the increased extravascular pressure caused by division of the mother cells of this group." [1e]

The energizing force to hematopoiesis may be a common one for all types of marrow-derived blood cells, or there may exist separate stimuli for the several blood elements. Chemotaxis is believed to play an important rôle in leukogenesis. Most of the infectious processes, particularly those of coccal origin, are attended by a leukocytosis of the neutrophilic order. Hemorrhage stimulates the production of blood platelets. The work of Minot and Murphy,[3] Peabody,[4] Castle,[5] and others has greatly advanced the knowledge of erythropoiesis by establishing the relationship of gastric physiology and certain dietary elements derived from proteins to the normal maturation of the megaloblasts of the bone marrow. This concept has been carried a theoretic step further by Witts [6] who maintains that vitamin C, thyroxin, iron, and traces of other metals are required to change the normoblast to the mature erythrocyte. Especial interest in the present connection relates to the normal stimulus to erythropoiesis. Granting the validity of the revolutionary observations above related, Bunting's contention of a constant tempo of red blood cell production [1e] still appears sound. He holds that a given quantum of bone marrow can only produce erythrocytes at a given rate. For an increased production there must occur an extension of the erythrogenetic centers. So far as is known, lowered oxygen tension constitutes the only normal stimulus to the extension of the bone marrow.[7]

Depression of hematopoiesis has long been recognized in diseases intrinsic and extrinsic to the bone marrow. This circumstance may arise from a primary disease of the myeloid system, or this important structure may be secondarily involved. The earliest available reference to the term, marrow insufficiency, by Vaquez and Aubertin,[8] follows: *"Étant donnée cette absence complète de réaction myéloide, nous fûmes amenés à penser que les organes hématopoietiques étaient incapables de former des globules rouges nouveaux, et nous portâmes—avec quelques réserves cependant—le diagnostic d'anémie pernicieuse avec moelle jaune, c'est àdire avec insufficance médullaire."* * Obviously, from the clinical course and the pathologic findings, these observers were dealing with a case of aplastic anemia in an adolescent offspring of a syphilitic and alcoholic parent. Their further analysis of the anemias by the bone marrow responses is illuminating. "Orthoplastic" anemia succeeds hemorrhage, and the marrow shows a normal response with some changes in the form and staining reaction of the erythrocytes, and a few nucleated forms appear in the peripheral blood. "Metaplastic" anemia is best exemplified in pernicious anemia where many nucleated red blood cells are seen, and megaloblasts and other signs of immaturity are not uncommon. Finally, the "aplastic" type is described as

* Because of this complete absence of myeloid reaction we were led to infer that the hematopoietic organs were incapable of forming new red blood cells, and we made the diagnosis—with some reservations—of pernicious anemia with yellow bone marrow, that is, with marrow insufficiency.

"un état fonctionnel insuffisant héréditaire ou acquis des organes hématopoietiques." *

Aplastic anemia was first recognized as a clinical entity by Ehrlich [9] in 1888. Most of the reported cases have resulted from exposure to the toxic action of radium, roentgen-ray, benzol, or arsphenamine. Occasionally an infectious process may lead to total paralysis or insufficiency of the bone marrow. In rare instances aplasia may appear in the course of an Addisonian anemia. Finally there remains an idiopathic type in which no etiologic background can be ascribed. The clinical course of the so-called idiopathic aplastic anemia is usually terminated by death within three months from the outset regardless of therapy. It occurs most frequently between the ages of 15 and 30 and more commonly in the female sex. A waxen pallor supervenes. Of particular differential value are the blood studies. The characteristic absence or extreme paucity of evidences of regeneration is the most important single detail. There may be little change in the individual erythrocytes. As contrasted with pernicious anemia, no signs of hemolysis are detectable. Leukopenia is the rule. The neutrophiles are especially decreased and a relative lymphocytosis results. The platelets are reduced. By reason of the thrombocytopenia, purpuric manifestations sooner or later complicate the anemic picture. Accordingly, in order, all of the marrow-derived blood cells are depleted in the peripheral circulation. As might be anticipated, a strikingly acellular yellow marrow is found at necropsy in all but a few exceptions.[10]

Case I

F. W., a white German-born woman of 38, entered the hospital with a chief complaint of progressive weakness of six weeks' duration. Questioning elicited the further complaints of increasing pallor, headaches frequently during the two months before admission, occasional tinnitus and vertigo, rather easy bruising but no spontaneous subcutaneous hemorrhages, one recent nose-bleed and occasional slight streaking of the sputum with blood. The patient worked as an ironer in a laundry. In an adjoining room carbon tetrachloride was used for cleaning. There were some fumes of carbon tetrachloride permeating her work-room; but she had no direct contact with any chemical. No fellow-employees experienced similar complaints and the family history was negative in this direction. The social and past histories were otherwise irrelevant.

The pertinent physical findings were moderate obesity, pallor of the skin and mucous membranes, three small petechial hemorrhages in the mucous membrane of the mouth, soft systolic murmur at the cardiac apex, slight edema of the lower extremities, small ecchymotic areas on the right arm and thigh and a few hemorrhages in the optic fundi.

The laboratory examinations included an urinalysis showing a slight trace of albumin and an occasional white blood cell. The blood chemical tests were normal, and the blood Wassermann test negative. The blood count showed a hemoglobin of 20 per cent, erythrocytes 1,570,000, leukocytes 3,600, neutrophiles 38 per cent, eosinophiles 4 per cent, and lymphocytes 58 per cent. Platelets were moderately decreased.

* A state of functional insufficiency of the hematopoietic organs, of either hereditary or acquired nature.

Bleeding time was 12 minutes; clotting time, 2 minutes. The fragility of the red blood cells was normal. Gastric analysis after histamine showed an absence of free acid. Stool examinations were negative.

During residence in the hospital, for 88 days, the patient had several small nosebleeds. Moderate fever existed irregularly. The patient was given liver extract 343 (Eli Lilly) for two weeks without improvement. Likewise, the daily administration of 90 grains of ferrous carbonate for over a month was without demonstrable effect. After repeated transfusions, the hemoglobin on the seventy-third hospital day was 51 per cent with 2,750,000 erythrocytes. Thereafter there was progressive decline in the red count and hemoglobin, and she was not capable of maintaining a level despite repeated transfusions of 500 c.c. of blood. During her residence in the hospital the patient had a total of 18 blood transfusions, each 500 to 600 c.c. in volume. Toward the end of her course, after four transfusions on four consecutive days, the hemoglobin was 31 per cent and the red blood cells numbered 1,700,000.

On the eighty-eighth day the patient's condition suddenly became alarming; there were hemorrhages from the gums; pulmonary edema supervened, subcutaneous edema rapidly became generalized, and the patient expired.

The postmortem examination showed hemorrhages into the gums, myocardium, ovary, and mucosa of the stomach, intestine and bladder, enlargement of bronchial lymph nodes, terminal bronchopneumonia, cardiac hypertrophy and dilatation, and an aplastic bone marrow. Microscopic examination showed hemorrhage in the lungs and in the bronchial lymph nodes in addition to the above mentioned sites. Microscopic examination of the bone marrow confirmed the gross evidences of aplasia.

The primary diagnosis was aplastic anemia of undetermined origin. The inconsiderable exposure to carbon tetrachloride probably played no part in the picture. The early hemorrhagic tendency bespoke a failure in the platelet formation as well as in erythropoiesis. The clinical course, laboratory, and necropsy findings sustained the primary diagnosis of an idiopathic aplastic anemia.

In a number of cases of aplastic anemia the impression of a congenital deficiency is gathered. Predtechensky [11] holds that congenital hypoplasia of the bone marrow is the precursor of primary aplastic anemia in event of an unusual demand for myeloid activity. Minot [12] entertains the same thesis in explanation for certain borderline cases between aplastic anemia and purpura hemorrhagica but prefers the designation, insufficiency of the marrow, with a qualifying phrase as to the particularly deficient element or elements. Rennie [13] suggests " that aplastic anemia in young persons is the result of the exhaustion of function of a bone marrow congenitally defective in power of endurance." In a different relation Miloslavich and Murphy [14] refer to the " constitutional (functional) inferiority of the bone marrow " that becomes completely exhausted under demand. Case 2 presents such a problem in pathogenesis.

Case II

E. G., a 63-year-old woman, herein considered through the courtesy of Dr. Frank L. Weston, gave the following story: All of her life she had had ecchymotic areas in the subcutaneous tissues after slight injuries. At times, even wiping the hands with a towel would produce hemorrhagic areas in the skin. Bleeding from the gums usually attended brushing of the teeth. Interestingly and pertinently, her

mother and sister were similarly affected. The patient had experienced colds and tonsillitis many times. Ten years before admission she had a rather profuse hemorrhage for three or four hours following dental extraction. Two weeks before admission the patient noted numerous purpuric areas over the legs, arms, and shoulders At the same time there was spontaneous bleeding from the nose and gums. There had been no fever, pain or soreness, and there was no known bleeding from any of the viscera.

The past medical history brought out nothing of importance. The menopause had occurred 13 years before.

The physical examination showed a fairly well developed and nourished female in apparent distress. Pallor was marked and over the limbs there were hundreds of subcutaneous hemorrhagic areas ranging from pinpoint to hand size. There were also some hemorrhagic areas on the face and trunk, one petechia in the conjunctiva and some in the oral mucous membranes. There was intranasal crusting due to dried blood. Of the two hemorrhagic areas on the tongue, the larger was 1 by 3 cm. in size. The lungs were clear; there was a systolic murmur localized to the cardiac apex; the blood pressure was 180 systolic, 102 diastolic. There was no adenopathy, and the spleen was not enlarged. On admission, the temperature was 100, pulse rate 120, respirations 22.

The laboratory examinations on admission showed a normal urinalysis, the nonprotein nitrogen and blood sugar within normal limits, blood Wassermann negative, stool examination positive for blood. The blood showed a hemoglobin of 55 per cent, erythrocytes 3,190,000, leukocytes 3,300 with 31 per cent neutrophiles, 3 per cent eosinophiles, 62 per cent small lymphocytes and 2 per cent large mononuclears. Blood platelets numbered 40,000. The coagulation time was 3½ minutes, bleeding time 40 minutes.

During residence in the hospital, the patient's course was that of progressive decline. A fever, reaching a daily peak of from 100 to 101° F., was the rule, and on the last two days before death the temperature rose to 105.2° each evening. Blood appeared in the urine on the third day after admission. After four transfusions of cross-matched, group IV (Moss) blood, the hemoglobin rose to 70 per cent, erythrocytes 4,280,000. The leukocytes ranged between 1000 and 2000 for the week before death, and there was always a relative lymphocytosis. The leukopenia had become more marked as the disease progressed, and reached a low level of 750 with 100 per cent lymphocytes on the day of death. The day after the second transfusion, the platelet count was 240,000; but save for one other day, again after a transfusion, the platelet count was invariably below 100,000 and most of the 16 days in residence the platelet count was between 20 and 40,000.

The postmortem examination showed in addition to multiple hemorrhages in the skin, lungs, pleurae, pericardium, stomach, kidneys, and bladder, a chronic gastritis and colitis, acute ulcers of the ileum and colon, pulmonary infarcts and in the main, an aplastic bone marrow. The rib marrow showed death of the leukogenetic centers; the erythrogenetic centers showed some nucleated red cells and intermediate types. The marrow was fatty; there was congestion and hemorrhage and an absence of megakaryocytes.

The final primary diagnosis was aplastic anemia. The etiology was undetermined. Dr. C. H. Bunting, who examined the microscopic sections, emphasized the existence of the gastritis and colitis and considered these abnormalities as possible etiological factors. Gastric analysis had not been made because of the patient's serious condition.

The hemorrhagic tendency in other members of the family raises the question of a congenitally defective bone marrow in this patient. Having

experienced a purpuric tendency from early life, the terminal course of her blood picture would suggest a progressive failure of the bone marrow to produce all of the common myeloid elements. After the sharp exacerbation of the chronic platelet deficiency, as manifest by the unusual bleeding, the marked anemia indicated an inhibition of the erythrogenetic function of the marrow, and finally the absolute neutropenia rendered the picture of marrow insufficiency complete in the failure of the leukogenetic centers.

In the so-called idiopathic aplastic anemia the prognosis is universally grave. A few subjects have experienced short remissions and then relapsed to a fatal termination as in the case reported by Larrabee.[15] Lescher and Hubble [16] collected five instances from the literature in which remissions had occurred in the course of aplastic anemia. Two of this series relapsed to death. No form of treatment avails. Gottlieb [17] performed a splenectomy upon a single patient with aplastic anemia or "complete myeloid insufficiency." An incomplete remission ensued and in spite of the fatal outcome, certain hematopoietic returns in his opinion justify a further consideration of the principle involved. Rendu and Widal [18] maintain that overactivity of the splenic function depresses the bone marrow. Their hypothesis is built upon a single case in which polycythemia attended tuberculous splenomegaly, and they admit the experimental and clinical evidence to the contrary in the absence of a polycythemia after splenectomy. Gottlieb [17] cites more substantial evidence of the inhibitory effect of the reticulo-endothelial system upon the marrow, as, for example, the leukopenia, anemia, and purpura that attend typhoid fever, influenza, and other infections with reticulo-endothelial hyperplasia.

The appreciation of general marrow insufficiency leads naturally to a consideration of the possible independent or selective involvement of one or the other of its component elements. Minot,[12] Rosenthal,[19] Lescher and Hubble,[16] Aubertin [20] and Gil [21] among others have indicated the liability of the several circulating blood cells to suffer independent depletion as a result of selective depression of their centers in the bone marrow. The growth of this viewpoint may be traced in a chronologic investigation of the literature. As a direct outgrowth of this movement, certain clinical entities have been evolved; but there remain many borderline cases that demand attention. Clearly, in the light of the histogenesis of the several blood cells an overlapping of the resultant hematologic pictures may be anticipated. Many terms have arisen to express such combinations. The *aleukia hemorrhagica* of Frank [22] is such an example. As the author explains, there is primarily a "myelotoxikose" with a secondary anemia, partially posthemorrhagic and partially myelophthisic. On careful analysis it would not appear a justifiable deviation from the generic term, aplastic anemia. The marrow biopsies of Falconer and Morris [23] indicate that invaluable though such studies may be, they are not infallible in the differentiation and definition of the basic fault. They plead for a more flexible nomenclature in contrast to Witts [10] who deems it "best to group all these cases under the broad heading

of aplastic anemia, as the leading feature in all is absence of regeneration on the part of the bone marrow."

The consideration of the clinical syndromes dependent upon failure of hematopoiesis in a single element of the marrow opens a number of interesting questions. The entire subject has been comprehensively treated by Lescher and Hubble,[16] who point out the striking infrequence of pure red cell anemia. They found only three cases in the literature. From a theoretic as well as a working viewpoint, the term, anerythropoietic is herewith suggested, for this limited group in which only the erythrogenetic centers suffer. Such a designation is an obvious adaptation of Hayem's *anémie par anhématopoièse* which Aubertin [24] thus described: "*C'est pourquoi, quand on parle aujourd'hui d'anémie par anhématopoièse, il s'agit d'anémie par insuffisance de la moelle osseuse, ou plus exactement du tissu myéloïde, insuffisance totalle ou partielle, ou mème simple déviation fonctionelle de ce tissu.*" * Unquestionably a majority of such patients pass into a more or less complete marrow failure with a resultant picture of idiopathic aplastic anemia as Aubertin [24] suggests.

Greater opportunity to study the results of the depression of thrombocytopoiesis and of leukopoiesis has been afforded by the more abundant clinical materials. The reduction of the blood platelets may occur from many causes. In the present relation only essential thrombocytopenia is considered. The most conspicuous detail in its clinical picture is the hemorrhagic tendency. Minot [12] sets 60,000 per cubic millimeter as the critical level below which reduction of the platelets is attended by bleeding. In the purpura hemorrhagica that attends this condition, bleeding occurs into the skin and mucous membranes with frank epistaxis, hemoptysis, hematemesis, melena, hematuria at times. Menorrhagia and metrorrhagia present serious problems in blood loss in females with this condition. Cerebral hemorrhage is not common. From the laboratory viewpoints in addition to the more or less marked reduction of the platelets, a hypochromic anemia is the rule. The bleeding time is almost invariably prolonged. The clotting time is approximately normal. The resultant coagulum is poor in texture and retracts very inadequately. The tourniquet test, although commonly positive, offers little aid in diagnosis because of its presence so widely in hemorrhagic affections. Falconer and Morris [23] question the wisdom of marrow biopsies in purpura hemorrhagica.

The following case is a classical instance of thrombocytopenia in all essential details:

CASE III

E. T., a white female aged 27 years, was first seen in consultation with the late Dr. Louis R. Head in January 1929. Throughout her life she had remarked easy bruising upon slight trauma. Two paternal cousins had a similar tendency, and one

* Therefore when we speak now of anemia due to an hematopoiesis we mean anemia due to insufficiency of the bone marrow or more exactly of the marrow tissue; and this insufficiency may be total or partial, or even be only a functional deviation of this tissue.

had had a splenectomy to remedy this condition. The patient's present complaint was dated to June 1927, when she had first observed profuse menstrual bleeding. Ten to twelve pads had been used daily through each menstrual cycle since that time. In December 1928, the patient had suffered an attack of influenza, and after about a month (or upon the initiation of the next menstrual cycle) there was profound menorrhagia succeeded by severe and recurrent epistaxis. Shortly there appeared large purpuric areas over both legs and smaller ones on the arms. The mucous membrane of the mouth was studded with similar lesions.

The failure of minor measures to control the situation and the development of a profound anemia led to her admission to the Madison General Hospital on January 29, 1929.* The blood count on January 28, 1929, immediately before entrance, was as follows: Hæmoglobin 45 per cent, erythrocytes 1,750,000, leukocytes 9,000; differential count, neutrophiles 81 per cent, eosinophiles 1 per cent, lymphocytes 15 per cent, mononuclears 3 per cent. The platelets were observed to be very markedly reduced in this study and the first numerical count was recorded three days later as 40,000 per cubic millimeter. The trend of these elements through the two periods of hospitalization is plotted in figure 2.

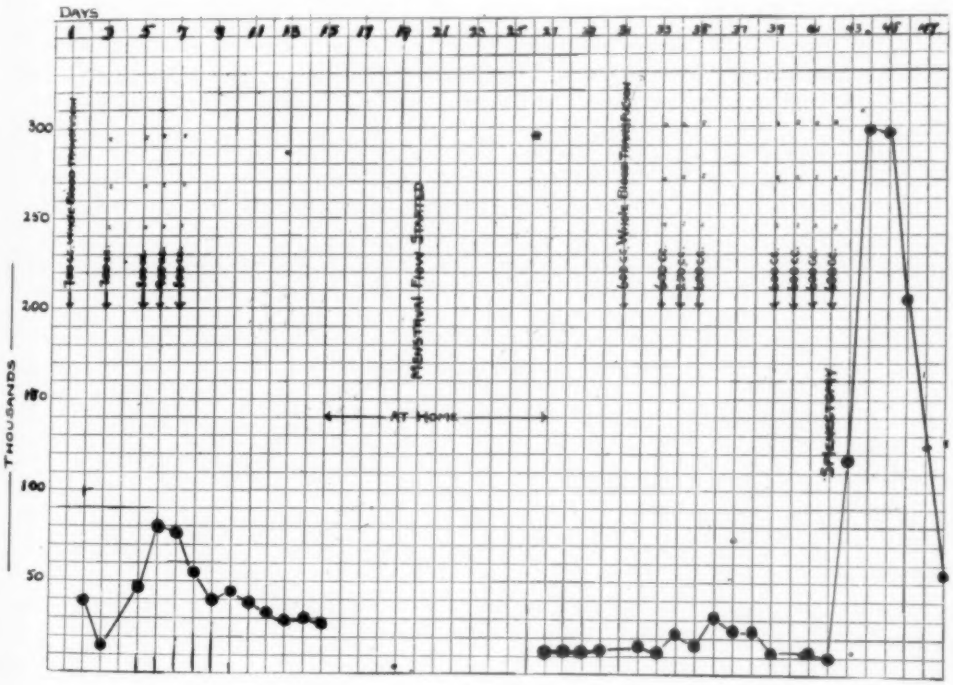


FIG. 2. The curve of the blood platelets in Case 3.

Particular attention is directed to the very transient advantage of the repeated (5) transfusions during the first period of hospitalization. Although bleeding was controlled at this time, with the next menstrual cycle all of the purpuric manifestations recurred in an aggravated form. Whereupon no material benefit in the bleeding tendency resulted from the multiple (8) transfusions which merely served the purpose of modifying the severity of the anemia through replacement. Subsequent to the

* We are indebted to Dr. Lester McGary for the laboratory studies during the patient's stay in this institution.

splenectomy performed by Dr. N. M. Percy of Chicago, the platelets rose from 10,000 to 118,000 on the first day, and to 299,000 on the second day postoperatively. This level was not maintained, for a week after the operation the platelets numbered 55,000 and 10 days later (17 days postoperatively) 24,400. Nevertheless, the control of bleeding was spectacular. For the first three days after the operation there was a small amount of vaginal bleeding. Thereafter, none appeared. On the ninth day postoperatively there was a slight epistaxis which was easily controlled.

Dr. Lester McGary gave the following description of the spleen: The organ measured 13.5 by 6.5 by 4.5 cm. and weighed 195 gm. The capsule was smooth and moist and of normal thickness. Two small infarcts, size of ten-penny nail, were seen on the anterior inferior surface. The cut surface was smooth and reddish brown in color. The Malpighian corpuscles and trabeculae were distinct. Sections showed an increase in endothelial cells and eosinophiles.

A year of freedom from any purpuric manifestations followed the splenectomy. Then in March 1930, menorrhagia recurred and purpuric spots appeared on the arms, hands, forehead, and neck. Interestingly this episode succeeded a period of intensive whole liver therapy. On April 1, 1930 she was admitted to the Wisconsin General Hospital where the platelets were found to number 30,000 per cubic millimeter. A transfusion of 500 c.c. of whole blood caused a sharp reaction with the temperature rising to 104° F. Thereafter the platelets ranged from 60,000 to 150,000, and the patient was discharged on April 16 with the hemorrhagic tendency under control.

During the ensuing two years she was under constant observation, and at no time was there a relapse in the blood picture or evidence of unusual bleeding. The platelets mounted as high as 310,000 on July 6, 1931, and at no time fell to critical levels. The menstrual flow remained rather scanty. Her activities were gradually extended; and after consultation and complete discussion as to the hazards, pregnancy was sanctioned early in 1932. The platelets were followed closely through gestation and ranged from 110,000 to 140,000 until the day before delivery when they fell to 50,000. Apparently coincident with this decline in the platelets, there appeared many purpuric spots over the face and body. Ten days after delivery, the mother's platelets had mounted to 140,000, and five weeks later to 220,000. Subsequent to this time there has been no recrudescence in the purpura. The baby was normal in all details.

This patient represents a clear-cut example of thrombocytopenic purpura of the idiopathic variety since no cause could be determined. The response to splenectomy was truly dramatic, and, as pointed out by many observers, the resultant advantage was maintained even though the platelets fell to precarious levels shortly after the operation. The relapses, a year postoperatively and immediately before parturition, were quite transient. The first episode apparently responded to the severe transfusion reaction. In any event this circumstance initiated the improvement which held the hemorrhagic tendency in check until just before delivery. Whatever may have been the factors determining the very transitory purpuric manifestations on the latter occasion, there was no unusual bleeding at parturition and no occurrence of the purpura thereafter. To the present time there has been no further recurrence of the bleeding.

The prognosis of essential thrombocytopenia varies widely. At times simple measures in hemostasis will tide over relatively slight episodes of bleeding. Again transfusions will meet the exigencies of the given case. It is well to remember that the life of the platelet is three to five days.[12] Hence, an advantage prolonged for an interval exceeding this short period

after transfusion must be attributable to the patient's own recuperative powers. Minot [12] points out that, as a rule, if the marrow fails completely, the platelets will be the first element to disappear from the circulating blood.

The treatment of thrombocytopenia is by no means standardized. Dietary measures, liver, vitamins, especially A, B, and C, viosterol, minerals, including iron and calcium, and ultra-violet light therapy have been recommended. A rational regimen of living and eating seems reasonable; but no specific virtue has been found in any single therapeutic agent. Splenectomy is indicated upon the failure of simpler means to control the fundamental fault. It should not be withheld until the hazard of the operation is overwhelmingly increased by the gravity of the bleeding or the anemia. Leukopenia and the absence of active hematopoiesis are relative contraindications to splenectomy in this condition.[16] Ligation of the splenic artery has not been universally successful as a substitute for removal of the spleen.[25] Roentgen-ray therapy over the splenic areas has not satisfactorily supplanted splenectomy in the experience of most clinicians. The favorable responses to splenectomy are not uniform. Christian [26] believes it impossible to predict the outcome of the operation. It should, nevertheless, be given full consideration with the reservations as stated.

Failure of leukopoiesis was first reported as a clinical complication of severe sepsis by Türk [27] in 1907. It has been recognized as a portent of serious marrow insufficiency in overwhelming infections since that time. The clinical syndrome of agranulocytosis or agranulocytic angina was described and named by Schultz [28] in 1922. For a time a controversy waged as to the sequence of events. At present, it is generally accepted that necrosis occurs subsequent to the depletion of the circulating neutrophiles. In a number of reported instances a neutropenia has developed some days antecedent to the appearance of the anginal symptoms. In the typical case there appears a period of malaise and physical depression before the frank febrile bout. Then the patient becomes markedly prostrated, the temperature rises to 101 to 105° F., and areas of necrosis appear in the mouth, rectum, or vagina. The draining regional lymph nodes may become enlarged; but general lymphadenopathy and splenomegaly are not the rule. The blood picture is extremely interesting. In a majority of cases the leukocyte picture alone is affected. Philiptschenko [29] proposes three groups of cases with failure of leukopoiesis; but his inclusion of patients with anemia and with anemia plus hemorrhage involves the consideration of the complicated pictures, previously discussed. Weber [30] also maintains that there is no definite boundary between agranulocytosis and aplastic anemia; but as a matter of fact, the usual neutropenia shows neither anemia nor hemorrhagic tendency. At times an advanced or terminal case may evidence extension of the marrow insufficiency by these manifestations. The usual patient with neutropenia shows a gross decrease to total absence of these marrow-derived granular elements. The course of the basic condition may be traced by the percentage and numerical figures for the neutrophilic

polymorphonuclear leukocytes. With their continued depletion there is serious danger of complicating pyogenic processes in the lungs and urinary tract as well as the above mentioned necrosis in passages directly connected with the exterior. The dependence of the mucous membranes of the mouth, rectum, and vagina upon the mobile protection of the neutrophiles is in no manner better attested than in the rapid healing of necrotic areas in these locations upon the reappearance of the missing or deficient white blood cells. As a rule the bone marrow shows little or no leukogenetic activity at the height of the neutropenia, but Fitz-Hugh and Krumbhaar [31] have established cases of neutropenia with definite leukopoiesis in the marrow. They postulate the probable occurrence of a failure of maturation and delivery of the neutrophiles from such centers.

Especial interest in the neutropenias centers about the surpassing contribution of Madison and Squier [32] to its pathogenesis. In a well-controlled series of cases these clinicians establish the unquestionable responsibility of amidopyrine for a certain number of the neutropenic reactions. They feel that the neutropenia is a sensitization to the drug and that there are, of course, other and varied causes for the same failure in leukopoiesis by the bone marrow.

The following case quite vividly illustrates their position relative to amidopyrine's responsibility:

CASE IV

R. R., a white school-boy, 13 years of age, apparently slowly convalescing from rheumatic fever, was admitted to the Wisconsin General Hospital. The history was important only in the detail of the polycyclic order of the arthritic manifestations. The physical examination disclosed cryptic diseased tonsils, carious teeth, an apical systolic thrill and murmur, swelling, heat and redness of both knees. Studies of the blood revealed a minor degree of secondary anemia (erythrocytes 4,500,000; hemoglobin 70 per cent) and a slightly elevated white cell count (9,880 with 63 per cent neutrophiles). The early stay in the hospital was marked by satisfactory progress in the arthritic involvement, occasional slight elevations of temperature not exceeding a degree and improvement in the general condition for 28 days.

On the twenty-ninth day the patient experienced listlessness, general malaise, fever, and chills. There appeared an irregular, inconstant blotching of the skin, puffiness of the eye-lids and redness of the oro-pharynx. The temperature rose to 102° F. The leukocyte count, on the thirty-second day, was 10,300 with 51 per cent neutrophiles, 43 per cent small lymphocytes, 1 per cent large lymphocytes and 5 per cent large mononuclears.

In the belief that these manifestations represented a rheumatic recrudescence, amidopyrine was administered in doses of 5 grains four times a day. On the fourth day of this therapy and after a total of 45 grains, the patient complained of severe epigastric pain, and the temperature rose to 105.4° F. A number of petechiae appeared in the soft palate; the abdomen was tender and resistent, especially high in the epigastrium; the liver was palpable 4 cm. below the costal margin; the skin showed a blotchy macular eruption. The leukocytes numbered 3800 with 40 per cent neutrophiles, 52 per cent small lymphocytes, 5 per cent large mononuclears, and 3 per cent metamyelocytes. Thereafter, leukocyte and differential counts were made twice a day The curve is plotted below. (Figure 3.)

It will be observed that the marrow-derived white cells reached their lowest level on the day after the discontinuance of amidopyrine with 1 per cent neutrophiles and 6 per cent metamyelocytes, or 322 marrow-derived white cells in a total white cell count of 4600. The complete disappearance of neutrophiles two days later, when the total leukocytes numbered 3,350, was attended by the sharp accession in metamyelocytes, 23 per cent, or a total of 770 cells of marrow origin. In evaluating the influence of pentnucleotide in the result graphed above, the initiation of the myeloid reaction within 48 hours after the institution of this therapy anticipated the usual response which is not expected for 96 hours. This advantage was maintained, and

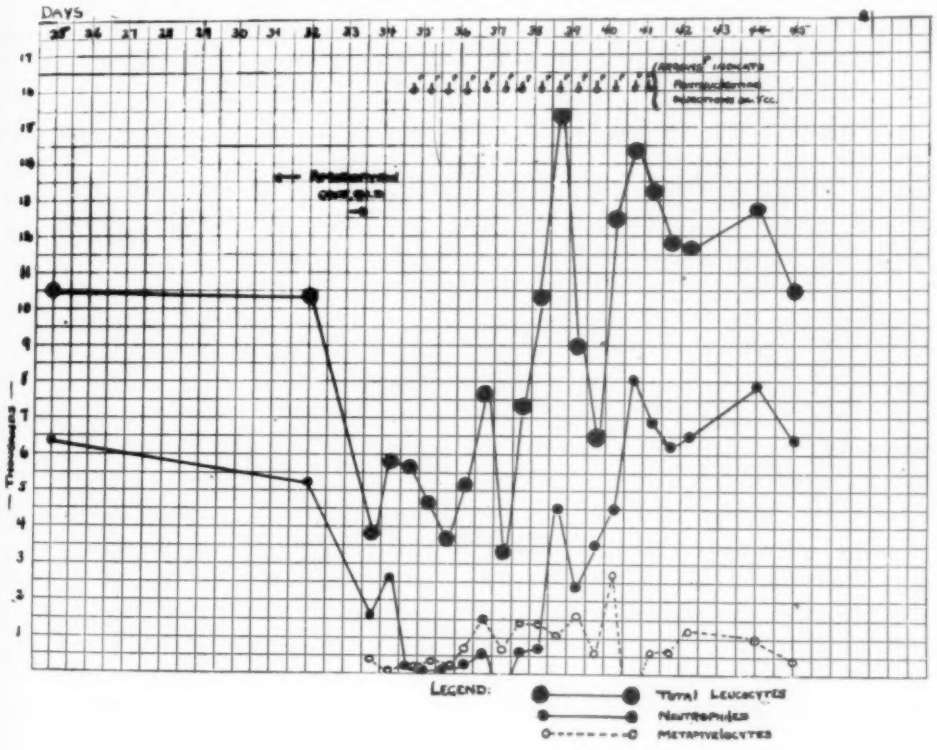


FIG. 3. The leukocyte curves in Case 4.

the temperature subsided to normal on the fourteenth day after the beginning of the neutropenic reaction. It is important to note that subsequent to a tonsillectomy on the ninety-second day of hospitalization, there was a reactive leukocytosis of 22,000, with 70 per cent neutrophiles.

This patient falls into the increasing group of neutropenias dependent upon a sensitivity to amidopyrine. The efficacy of pentnucleotide in this particular instance may be seriously questioned. In the first place, many reported cases of neutropenia of this order have recovered spontaneously and rapidly upon the withdrawal of amidopyrine. Furthermore, the initial evidence of leukogenetic response was remarkably prompt for a pentnucleotide effect. The apparently complete recovery of the leukogenetic centers

in the bone marrow is at least suggested by their later adequate response on the occasion of the tonsillectomy.

The prognosis in neutropenia depends in a considerable measure upon the existence of a recognizable and recognized cause. As remarked before, in subjects sensitive to amidopyrine, its removal is attended by prompt and maintained recovery. Idiopathic or essential neutropenia may undergo spontaneous or induced remissions. There is no regularity in the occurrence or duration of such remissions. Pentnucleotide in intramuscular doses of 10 c.c. twice daily is recommended.[33] Its administration must not be too early interrupted, since serious relapses may occur under these circumstances. The results in relapsing cases are frequently discouraging. Every precaution should therefore be taken to forestall serious declines in the circulating neutrophiles by appropriate doses of pentnucleotide. Adenine sulphate has given results similar to those attributed to pentnucleotide.[34] In the opinion of most students of the subject, small transfusions are of no specific value in neutropenia and large transfusions are contraindicated Roentgen-ray in small doses has been advised by certain observers but others seriously question its efficacy.

In conclusion, the clinical expressions of marrow insufficiency should always be borne in mind in the analysis of the blood dyscrasias. This important organ may fail as a unit, in which event the picture of aplastic anemia supervenes. Or any of its functional and histologic components may fail separately. Anerythropoietic (red blood cell) anemia is the rare condition, in which only the erythrogenetic function of the marrow is depressed. Thrombocytopenia results from the failure of the formation of blood platelets. Neutropenia may reflect a leukogenetic failure of the marrow. Lescher and Hubble[16] suggest the terms, myelophthisis, thrombophthisis, and granulophthisis, for aplastic anemia, thrombocytopenia, and neutropenia, respectively. These several clinical entities are interrelated, and their pictures may blend; but in the interest of clarity, they should be considered separately. Their pathogenesis and treatment take on peculiar significance from such an approach, and the solution of certain difficult problems in clinical hematology is promised thereby.

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III. THE METABOLIC ASPECT OF ASSOCIATED DIABETES MELLITUS AND PULMONARY TUBERCULOSIS *

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The association of tuberculosis and diabetes has attracted the attention of many authors and has been the subject of numerous case reports.† During the past five years, 80 patients presenting this combination of diseases have been under observation in Herman Kiefer Hospital, Detroit. A statistical analysis of the clinical features, prognosis and treatment of the tuberculosis as well as detailed reports of several cases have been published recently.[4, 5] Since there is no general agreement regarding the management of the diabetes complicated by tuberculosis and the effect of the pulmonary process upon the carbohydrate metabolism, we have felt that our experiences warrant discussion.

Selection of Cases. Thirty-two of the 80 cases were selected for nutritional study. Each of this group was under observation in the hospital for six or more consecutive months, the average length of stay being 555 days. All seldom or never refused any portion of the meals served to them and none, we believe, obtained additional food elsewhere. Limitation of the group selected for nutritional studies in this manner was considered necessary to minimize the many sources of error inherent in clinical work of this type.

The group included five in the third decade of life, six in the fourth, ten in the fifth, eight in the sixth, and three in the seventh. The sex distribution was about equal, there being 15 males, and 17 females. Twenty-six were white and six were colored.

Clinical Findings

Symptoms of Diabetes. The most frequent complaints were weakness and loss of weight, presumably because they are symptoms common to both diseases. Twenty-nine patients complained of weakness; 25 had lost more than 5 kg. (11 lbs.) in weight; the appetite, however, was preserved or increased in 24. Eighteen patients had had polydipsia and polyuria prior to entry, suggesting that the diabetes was grossly out of control.

Symptoms and Signs of Tuberculosis. The incidence of fever, night sweats, pleurisy, cough, sputum and hemoptysis in the entire group of 80 cases was given in a previous publication.[4] It was found that these symp-

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† Those in search of a review of the literature are referred to the articles of Root,[1] Banyai [2] and Scholz.[3]

toms occurred about as frequently in this series as in nondiabetic tuberculosis. Likewise the physical signs were in accord with the roentgen-ray findings in the majority of cases. The high incidence of symptoms and pathognomonic signs is contrary to the experience of Joslin [6] who stated that tuberculosis comes on more insidiously in the diabetic than in the general population. These differences in opinion may be due to differences in the type and extent of the tuberculosis. The pulmonary process in 27 of our cases was classified by the admission roentgen-ray as far advanced and in five as moderately advanced. The lesion was predominantly exudative in six, productive in 11, and mixed in 15. Cavitation was demonstrable in 29 of the 32 cases. Tubercle bacilli were found in the sputa of all but two patients, both of whom had had positive sputa previously at another hospital.

Laboratory. Urine examinations were made daily. In all of those consistently sugar free, 24 hour specimens were obtained. When there was a persistent or intermittent glycosuria, quantitative analysis was made on four fractional specimens, collected as follows: (1) from breakfast to dinner, (2) from dinner to supper, (3) from supper to bedtime, (4) from bedtime to breakfast. Blood sugars were taken at least once weekly in the following rotation: first week, before breakfast; second week, 2½ hours after breakfast; third week, 2½ hours after dinner; fourth week, before breakfast, etc. The Folin-Wu method of analysis was used. The diabetes was considered under control when the urine was constantly sugar free and the blood sugar was under 140 mg. per cent at all of these periods. It was considered out of control when either a consistent glycosuria or hyperglycemia (above 160 mg. per cent) occurred. It was regarded as under partial control when the blood sugar was between 140 and 160 mg. per cent. According to these criteria, all 32 patients were out of control on admission, whereas six were partially controlled and only one was out of control at discharge. The latter, who died in the hospital, had a marked hyperglycemia and glycosuria for two weeks prior to his death. The blood CO_2 combining power, however, was 62 vol. per cent on the day preceding exitus. The diabetes was controlled or partially controlled for more than three-fourths of the period of hospitalization in 11 cases, during ½ to ¾ of the period in 18 cases, during ¼ to ½ of the period in two cases and for less than ¼ of the period in one case.

Treatment of Diabetes

Preparation of Diets. All diabetic diets were prepared in a special kitchen under the supervision of a competent metabolic dietitian. The trays were checked by the dietitian before they were distributed to the patients and again on their return. All untouched food was weighed and replaced by something with an identical glucose equivalent. An especial effort was made to prepare palatable food and to cater to the likes and dislikes of the patients so that everything served would be eaten, leaving little temptation

to cheat. Precautions were nevertheless taken to minimize opportunities for obtaining food elsewhere. The patients were segregated from the non-diabetics in single and double rooms and were bed-fast for most of their hospital stay. Visiting hours were held four times weekly and visitors were not allowed to bring in anything edible. This latter rule was strictly enforced by the nurse escorting them to the patients' rooms.

Because of these precautions it is believed that the diets prescribed for the patients were for the most part identical with those actually consumed. The figures given for the composition of the diet represent carefully computed averages for the entire period of hospital stay.

Caloric Intake. The caloric intake of each patient is indicated in table 1, the average for the entire group being 2138 calories daily, or 34 calories per kg. On the other hand, the average house diet served to the routine cases of tuberculosis contained from 2500 to 3000 calories.

TABLE I

Average Caloric Intake during Period of Hospitalization

Total calories	1600–1800	1800–2000	2000–2200	2200–2400	2400–2600	2600–2800
No. cases	2	6	11	9	3	1
Total Calories						
Cal. per kg.	20–24	25–29	30–34	35–39	40–44	45–49
No. cases	0	5	14	9	4	0
Calories per Kg. Body Weight in Diet						
Cal. per kg.	20–24	25–29	30–34	35–39	40–44	45–49
No. cases	0	7	18	6	1	0

Calories per Kg. Required to Maintain Body Weight at a Constant Level

Weight. Since the caloric intake in these patients was distinctly less than is generally considered advisable in tuberculosis, the changes in body weight are presented in table 2. The patients were weighed routinely once or twice weekly under standard conditions on scales accurate to .25 kg.

As is evident in table 2, 23 were below the average weight for their height, age and sex on admission to the hospital and only four were above. A deliberate attempt was made to bring all patients to or slightly above the average. This was achieved in all but eight, six of whom are still in the hospital. The greatest weight gain during the period of hospitalization was 28.2 kg. (61.5 lbs.) on a daily intake of 2290 calories. The average weight gain for the entire group was 7.4 kg. (16.25 lbs.) on a diet containing 2138 calories. One patient who was considerably overweight on admission was

TABLE II

Body Weight

	Loss		Stationary	Gain			
Wt. in kg.	−25 to −15	−15 to −5	−5 to +5	+5 to +10	+10 to +15	+15 to +25	+25 to +35
No. cases	1	0	9	9	10	2	1

Change in Weight during Period of Hospitalization

	Below standard			At standard	Above standard		
	−35 to −25%	−25 to −15%	−15 to −5%	−5 to +5%	+5 to +15%	+15 to +25%	+25 to +35%
At beginning	4	8	11	5	3	0	1
At end	0	1	7	15	7	2	0

Weight in Percentage of Standard at Beginning and End of Period of Hospitalization

gradually reduced to her standard weight. This was later regretted because the tuberculosis became worse and exitus occurred.

Energy Requirements. Since such comparatively low caloric diets were sufficient to permit a weight gain in most of the patients, it becomes of interest to determine the number of calories needed to maintain weight at a constant level, i.e., the energy requirement. This can be calculated roughly if we assume that all of the added weight is deposited as fat.

Such an assumption ignores the possibility that a portion of the weight increment may consist of protein tissue, water stored temporarily in the body or fecal matter retained in the colon. Since all of the patients had attained full growth and since all received comparatively low protein diets (about 1 gm. per kg.) we believe that the protein deposited was negligible. An average of two or three weight determinations at the beginning and end of the period was used to minimize the error introduced by fluctuations in stored water and retained feces.

For each gram of weight gained, 8.5 calories were deducted from the total amount consumed during the period of observation.* The corrected value for the total calories was then divided by the number of days in the period to obtain the daily energy requirement, which in one patient was about 1570 calories, in six ranged from 1600 to 1800 calories, in eight from 1800 to 2000, in ten from 2000 to 2200, in five from 2200 to 2400 and in two from 2400 to 2600 calories. These figures represent the basal requirement, together with increments arising from the specific dynamic action of food,

* Each gram of adipose tissue deposited in the body contains about 0.1 gram of water. Thus its caloric yield is 0.9 that of pure fat (9.4 calories times 0.9 equals 8.5 calories).

from the activity of the patient and from the effect of the disease itself (through fever, etc.).

To analyze further these figures, the basal requirement was computed from the age, sex, height and average weight, using the charts of Boothby and Sandiford. The energy requirements of these 32 patients, expressed in percentage over and above the basal and classified according to the amount of physical activity and average afternoon temperature throughout the entire hospital stay are given in table 3. This table affords only a rough approximation of the actual energy requirements because of potential errors in the inexact determinations of total caloric intake, body weight, amount of physical activity and mean body temperature, and in the unproved assumption that the weight changes are due entirely to deposition or disappearance of body fat.

TABLE III

Energy Requirements

Av. p.m. temperature for entire hospital stay	Activity during period of hospitalization	Energy requirement in % above basal calories			
		15–30%	30–45%	45–60%	Total
Normal	Bathroom privileges during less than one-half of period	6	7	1	14
	Bathroom privileges over more than one-half	1	3	0	4
	Bathroom privileges during entire stay	0	3	0	3
98.8–99.7	Bedfast during entire period	1	4	2	7
	Bathroom privileges for less than one-half	2	1	0	3
99.8–100.7		0	0	0	0
100.8–101.6	Bedfast entire period	0	0	1	1
	Total	10	18	4	32

For purposes of comparison, the energy requirement of a normal individual under similar conditions may be established from the experimental data of Lusk and others. To cover bodily activity and the specific dynamic action of food, one would expect, from their results, an increment of 15 to 20 per cent in normal individuals confined to bed, of 20 to 30 per cent for bathroom privileges over less than half of the period of hospitalization and of 30 to 45 per cent for bathroom privileges during the greater part or whole of the period. Since the energy requirements of the majority of cases of diabetic tuberculosis fell within the estimated range of normal, it would appear that neither disease uncomplicated by high temperature appreciably

increased the caloric needs of the patient. Similar conclusions for uncomplicated tuberculosis were reached 14 years ago by McCann and Barr.[7]

Composition of the Diet. The composition of the diets of each of the 32 patients is given in table 4. The average diet for the entire group contained

TABLE IV

Composition of Diet
(Figures Represent Number of Cases)

Amt. in grams	50–74	75–99	100–124	125–149	150–174	175–199	200+
Carbohydrate	1	6	16	6	3	0	0
Protein	30	2	0	0	0	0	0
Fat	0	0	2	7	13	7	3

108 grams carbohydrate, 62 grams protein, 162 grams fat and 160 grams available glucose.

Protein. Thirty patients received from 50 to 70 grams protein daily while two received 75 grams. In terms of average body weight, this amounted to between 0.8 gram and 1 gram per kilo in 20 cases, between 1 and 1.2 gram per kilo in 8 and between 1.2 and 1.35 gram per kilo in 4.

McCann [8] has pointed out that a diet containing the smallest amount of protein necessary to insure nitrogen equilibrium is desirable in tuberculosis, because the specific dynamic action of such a diet is at a minimum.

Nitrogen balance studies were carried out on two patients for six consecutive days. One was at bed rest with a slightly active lesion and had been receiving 0.8 gram protein and 30 calories per kilo for 10 months; the other was ambulatory with a quiescent lesion and had been receiving 1.1 gram protein and 32 calories per kilo for 13 months. The first patient consumed a total of 58.5 grams nitrogen over a period of six days and excreted a total of 49.5 grams in the urine and feces. The second consumed 68.8 grams and excreted 66.9 grams of nitrogen.* It thus appears that the protein of the diet in both cases was more than sufficient for the bodily needs.

Carbohydrate and Fat. The average diabetic diet contained 108 grams carbohydrate and 162 grams fat whereas the average house diet contained between 300 to 350 grams carbohydrate and between 120 to 150 grams fat. Studies are now in progress to determine, if possible, the ideal carbohydrate-fat ratio in diabetic tuberculosis. Though the data are insufficient to permit conclusions, they seem to indicate that a carbohydrate intake of 100 to 125 grams and a fat intake of 150 to 175 grams are about optimal. In this formula sufficient carbohydrate is provided to render the diet palatable and to insure the complete combustion of fat. Since the major portions of the calories come from fat, the pulmonary ventilation is considerably reduced (McCann [7]) with greater rest to the lungs as a consequence.

* Neither patient raised an appreciable quantity of sputum so that nitrogen loss through this source was considered negligible.

Insulin. The insulin requirements of each patient are given in table 5. The average amount of insulin needed to bring the patients under control on admission was 46 units daily whereas 42 units were required at discharge.

TABLE V

Insulin Required for Control of Diabetes
(Figures Refer to Number of Cases)

Units Insulin	0	1–10	11–24	25–49	50–74	75+
At beginning of hospital stay	3	4	2	6	14	3
At end	5	2	4	4	13	4

This does not give a correct impression of the changes in carbohydrate tolerance, since the average discharge diet contained considerably more available glucose than the average admission diet. Correcting for the excess available glucose on the hypothetical basis that 1 unit of insulin is equivalent to 2 grams of glucose, a figure of 34 units daily is obtained as the theoretical insulin requirement at discharge if the admission diet had been carried through.

The total daily insulin at the time of discharge was given in a single injection to four patients, in two doses to six, in three injections to eight, and in four doses to nine. The optimal time for a single daily dose of insulin was 15 to 30 minutes before breakfast; for a second dose, at a similar interval before supper; for a third dose, generally about midnight; and for a fourth dose, before the noon meal. Two patients were encountered who were better controlled when the insulin was given after meals.

DIABETIC MANAGEMENT AT THE TIME OF SURGICAL TREATMENT OF THE TUBERCULOSIS

Pneumothorax was induced in 22 of this group, phrenic surgery was performed in 18, pneumolysis and thoracoplasty in one each.*

Pneumothorax and phrenic operations were performed by the thoracic surgeon whenever indicated without consulting the physician in charge of the diabetes. Hyperglycemia and glycosuria often occurred on the day of the operation, but quickly disappeared unless a pleural effusion developed or secondary infection occurred.

Before each stage of the thoracoplasty was attempted, however, the diabetes was carefully controlled. Three hours before the operation was scheduled, the usual morning dose of insulin was given, together with the glucose equivalent of breakfast in some readily assimilable form (such as sweetened orange juice). As soon as the patient returned from the operat-

* Thoracoplasty has been successfully performed in another diabetic not included in this group of 32.

ing room, a urine specimen was obtained and analyzed for glucose. Insulin was then given subcutaneously in accordance with the results of the Benedict test, 20 to 25 units, if orange; 15 to 20, if yellow; 10 units, if green; 5 units, if blue. This was followed by the intravenous injection of 25 grams glucose in 250 to 500 c.c. saline. This procedure was repeated every four hours around the clock until the patient was able to take nourishment by mouth, when feedings containing a similar amount of available glucose were substituted for the intravenous glucose. After two or three days, provided the diabetes was under control, the patient was placed upon his preoperative dietary formula, divided into three or four highly concentrated feedings.

Results

Outcome of Tuberculosis. The results to date in the entire group of 80 cases, classified according to the criteria adopted by the National Tuberculosis Association have been discussed at length elsewhere.[4] At this time we will merely set down, in brief, the results in the 32 cases on which the nutritional studies have been based. Twenty-seven of the cases were classed as far advanced on admission and five as moderately advanced.

On April 1, 1934, seven of the group were dead, one was untraced and 24 were known to be alive. Nine of the latter were classed as arrested or apparently arrested, four as quiescent, four as improved and seven as unimproved. The deaths were all due to tuberculosis. None of those who died in the hospital showed a clinical degree of acidosis at death. Three moribund patients, not included among this group of 32, died during insulin reactions. In each instance it was felt that the reaction probably precipitated a death that was inevitable. Severe insulin reactions occurred in many whose strength was slightly or moderately impaired without threatening life.

Carbohydrate Tolerance. The available glucose in the diet in excess of the insulin required to keep the blood sugar below 140, calculated on the basis that 2 grams glucose are covered by 1 unit of insulin, may serve as an index of carbohydrate tolerance. Though this method is necessarily inaccurate, due to the fact that the insulin glucose equivalent varies within rather wide limits, it still furnishes a rough measure for evaluating improvement or retrogression in the diabetes. The glucose uncovered by insulin when the diabetes was first brought under control and again at discharge is given in table 6.

Table VI

Available Glucose in Diet in Excess of Insulin
(Calculated on Basis that 1 Unit of Insulin Is Equivalent to 2 Grams Glucose)

Grams glucose	−50 to 0	1–49	50–99	100–149	150–199	200+
At beginning of hospital stay	4	11	9	8	0	0
At end	3	11	5	8	3	2

The carbohydrate tolerance was regarded as markedly improved when there was an increase of more than 50 grams in the available glucose uncovered by insulin; slightly improved when there was an increase of from 15 to 49 grams, and unchanged when there was an increase or decrease of less than 15 grams. A decrease of from 15 to 49 grams was considered a slight fall in carbohydrate tolerance; a decrease of more than 50 grams, a marked fall. According to these criteria, the carbohydrate tolerance showed a marked improvement during the period of hospitalization in 11 cases; a slight improvement in four; no change in seven; a slight fall in four and a marked fall in six.

Effect of Tuberculosis upon Carbohydrate Tolerance. Twelve patients had been under observation in diabetic clinics prior to the onset of the tuberculosis.* Five of these showed a marked fall in tolerance with the advent of the tuberculosis, five showed a slight fall and two showed no appreciable change.

The effect of the tuberculosis upon the diabetes during hospitalization is given in table 7. The carbohydrate tolerance was determined in the manner described above at the beginning and end of a period in which there

TABLE VII

Effect of Tuberculosis on Carbohydrate Tolerance

Tuberculosis	Carbohydrate Tolerance					
	Markedly Improved +50 or more	Slightly Improved +15 to +49	Unchanged +14 to −14	Slightly Worse −15 to −49	Much Worse −50 or over	Total
Considerably improved	7	0	0	0	3	10
Slightly improved	4	6	4	3	0	17
Slightly worse	2	1	3	4	4	14
Much worse	3	1	3	1	1	9
Total	16	8	10	8	8	50

was a definite change, both in serial roentgen-rays and in constitutional symptoms. Several patients showed periods of improvement and retrogression in the tuberculosis and consequently are represented more than once in the table. It does not necessarily follow, of course, that the change in tuberculosis was responsible for the change in carbohydrate tolerance merely because the two were coincidental. However, care was taken to eliminate from consideration any period in which there was an obvious cause for

* We wish to acknowledge our indebtedness to Dr. F. B. Peck for his permission to use the Grace Hospital diabetic records.

the change in tolerance apart from the tuberculosis (for example intercurrent pyogenic infection, etc.). It is, of course, impossible to eliminate spontaneous fluctuations in tolerance independent of the tuberculosis.

In 27 instances, there was a parallel change in the tuberculosis and diabetes; in 17 cases, both showed improvement concurrently; in 10 cases, both became worse. In 13 instances the courses of the tuberculosis and diabetes were divergent. An improvement in tuberculosis was accompanied by a fall in carbohydrate tolerance in six cases, whereas the reverse occurred in seven.

Thus there appears to be no fixed rule governing the effect of tuberculosis upon coexistent diabetes. The courses of the two diseases are usually parallel but may be divergent.

An intercurrent pleural effusion, however, is generally accompanied by a temporary fall in tolerance. A marked fall in tolerance occurred coincidently with the development of an effusion in three cases, a slight fall in six, no appreciable change in three and a slight rise in only one.

Summary and Conclusions

1. This study is based upon a group of 32 patients with coexisting diabetes and tuberculosis, each of whom was in the hospital for six or more consecutive months, the average length of stay being 555 days.

2. The composition of the average diet for the entire group was as follows: carbohydrate 108 grams; protein 62 grams; fat 162 grams; available glucose 160 grams; total calories daily 2138. In comparison, the average house diet contained 2500 to 3000 calories apportioned as follows: 300 to 350 grams carbohydrate, 80 to 85 grams protein and 120 to 150 grams fat. Owing to its relatively higher fat and lower protein and carbohydrate content, the diabetic diet is theoretically more suited to the treatment of tuberculosis since less energy is dissipated in the digestion and assimilation of food and less pulmonary ventilation is required.

3. This diet furnished an average of 34 calories per kilo and was sufficient to permit an average weight gain of 7.4 kilos (16¼ lbs.). The energy requirements, calculated in percentage over and above the basal, fell within the estimated range of normal in the majority of cases of diabetic tuberculosis. It would thus appear that neither disease appreciably increased the caloric needs of the patient.

4. Nitrogen balance studies were done on two patients receiving 0.8 gram and 1.1 grams protein per kilo respectively. Both were in positive balance at the time of the studies.

5. The average amount of insulin required to control the diabetes was 46 units daily on admission and 42 units daily at discharge. There was a marked improvement in carbohydrate tolerance during the period of hospitalization in 11 cases, a slight improvement in four, no change in seven, a slight fall in four and a marked fall in six.

6. The tuberculosis was classed on admission as moderately advanced in five cases, and as far advanced in 27. Pneumothorax was induced in 22 of the group, phrenic surgery was performed in 18 and thoracoplasty in one. On April 1, 1934, seven of the group were dead, one was untraced and 24 were alive. Nine of the latter were classed as arrested or apparently arrested, four as quiescent, four as improved and seven as unimproved.

7. The course of the tuberculosis and diabetes was parallel in 67 per cent of the cases; in 42 per cent there was concurrent improvement in both diseases, and in 25 per cent concurrent retrogression. An improvement in tuberculosis was accompanied by a fall in carbohydrate tolerance in 15 per cent whereas the reverse occurred in 18 per cent. An intercurrent pleural effusion was generally accompanied by a temporary fall in tolerance.

Acknowledgment of our indebtedness is made to Dr. Samuel S. Altshuler for his aid in diabetic management; to the Superintendent of Herman Kiefer Hospital, Mr. George Phillips, and to the medical, surgical and dietetic staffs of the Tuberculosis Unit for their splendid coöperation.

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ERYTHREMIA *

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The clinical recognition of erythremia should no longer offer difficulty. Its essential features have been identified by Vaquez,[1] and the clinical syndrome made familiar since the descriptions by Osler.[2, 3] The finding of an enlarged spleen in a patient with generalized "red" cyanosis should bring to mind the diagnosis of erythremia. More commonly, splenomegaly is associated with diseases characterized by anemia. The clinical distinction of polycythemia vera becomes difficult when we see the occasional patient suffering from this disease who presents himself in the late stages with anemia [4] rather than polycythemia. The correct interpretation can then usually be made from the past history. Congenital heart disease at times produces a similar picture aside from the cardiopathy. We have recently encountered such a patient who exhibited an enlarged spleen in addition to a polycythemic blood picture. Where cyanosis and an increased red blood count are the result of pathologic changes in the lungs or pulmonary vessels, splenomegaly is, as a rule, not present and the respiratory symptoms help to identify the pathologic picture. When cyanosis is the result of mediastinal pressure due to new growth (lymphoblastoma) and there is concomitant involvement of the spleen with enlargement, the absence of an increased blood count differentiates the condition. In such cases the cyanosis is not generalized and not "red."

The case to be presented was observed between the years 1927 and 1932, and an opportunity was afforded to study the patient both clinically and pathologically. An episode of colonic bleeding and diarrhea, diagnosed as amebic colitis, was of particular interest because of its effect upon the blood counts.

Case Report

I. B. D. D., white, male, aged 65 years, occupation—civil engineer, had been employed in the tropics over long periods of time. He consulted us in 1927 complaining of substernal distress after meals. He had recently been told that he was suffering from an abnormal blood condition. There was no family history of other members suffering from this disease. He had had typhoid at the age of twenty-eight. In 1926 he had the first symptoms which led to the diagnosis of amebic dysentery.

On physical examination he presented the findings classical for erythremia: cyanosis, splenomegaly and polycythemia. The spleen was hard and smooth. The rounded edge was felt about four inches below the costal margin. The liver edge was at the costal margin. The blood pressure was: 140 mm. Hg systolic and 90 mm. Hg diastolic. The Wassermann reaction on the blood serum was negative. The electrocardiogram showed widening of the QRS complexes in all three leads, with an inverted T-wave in the first lead. The urine contained a heavy trace of albumin

* Received for publication January 12, 1935.

and showed 10 to 15 red blood cells per high power field. The blood counts are summarized in table 1, and the laboratory proceedings enumerated in table 2. A roentgen-ray of the colon after a barium enema revealed the displacement of that organ by the enlarged spleen.

TABLE I*

Blood Studies

Date	R.B.C.	W.B.C.	Hemoglobin	Platelets
3/27/1927	6,000,000	18,000	100%	
11/7/1927	7,552,000	15,600	110%	
1/14/1928	8,640,000	10,200	105%	
2/12/1929	4,120,000	10,000	85%	
6/12/1929	4,400,000	10,750	81%	
11/26/1930	7,960,000	30,700	126%	210,000
1/27/1931	8,860,000	25,750	130%	
2/17/1932	9,050,000	18,550	136%	
7/3/1932	7,980,000	12,720	135%	

* The blood counts were always elevated except during 1929, the lowered counts coinciding with the episode of colonic bleeding. In the differential count the polynuclear cells averaged about 90 per cent; there were no other variations from normal. No immature red cells or pathologic white cells were ever identified in the smears. The platelets appeared definitely diminished in numbers in proportion to the red cells, occurring singly or in small clumps with occasional giant forms.

TABLE II*

Laboratory Data

Bleeding time	7 minutes
Coagulation time	12 minutes (tube method)
Clot retraction	Firm after 6 hours with good separation of serum
Volume index	1.02
Blood serum calcium	16 mg. per 100 c.c.
Proportion of cells to plasma	Red cells 80% Plasma 20%
Red cell fragility test	Hemolysis began .48% saline Hemolysis complete .32% saline
Basal metabolism	Plus 49

* The important variations from normal were the increased basal metabolism and increased calcium, characteristic alterations in this disease. The proportion of red cells was markedly increased over their normal relation to plasma (48/52). The blood sugar and blood nitrogen elements were always within relatively normal limits, except for a terminal non-protein nitrogen of 70 mg. per cent.

The year 1927 was uneventful except for some mild arthritic pain in his right knee. He made a trip to Nicaragua and when he returned in 1928 his diarrhea became much more marked. It was not, however, bloody. *Entamœba histolytica*, both the encysted forms and motile protozoa, were found in his stools on several occasions —February 7 and March 6, 1928—and treatment was begun for amebiasis. This consisted of several courses of emetine hydrochloride, bismuth, yatren, and a careful diet. After several months these symptoms disappeared and did not recur. The stools were subsequently negative for entamebae.

In November 1930, after returning from South America, he reported several new episodes in the course of his disease. He had had several attacks of hematuria during the preceding August and had been advised to have roentgen-ray treatment. At that time his right knee and his great right toe had become swollen and tender. He now also complained of cramps in his legs at night.

On February 23, 1931, he had a profuse pulmonary hemorrhage following which

he was in shock. He responded well to morphine. It was then decided to give him some roentgen-ray treatment to his long bones and for this purpose he was referred to Dr. Leon T. Le Wald.

Small doses of roentgen-ray therapy were given over the long bones, using moderate voltage (120,000 K.V.), filtered through 4 mm. of aluminum at a 40 cm. distance, using from 50 to 100 milliampere minutes, repeated at intervals of from 3 to 14 days, between February 28 and July 14, 1931. Treatment was also administered to the spleen between April 21 and July 14, 1931, and one treatment to the liver was given on July 14, 1931. Treatment was given again to the long bones between March 8 and April 14, 1932, and one treatment to the spleen on March 14, and another on March 26, 1932, and one treatment to the liver on March 31, 1932.

On April 6, he again complained of pain in his feet and ankles and was relieved somewhat by aspirin and atophan. At this time he noted that he could mentally concentrate better and that he could do things that had previously been an effort. We felt that there was at least some clinical improvement from the roentgen-ray treatment he had received. On April 22, he developed a tender purpuric spot over the right hip, apparently a hemorrhage. In May again he complained of arthritis. Unsuccessful attempts were made to relieve this by removal of foci of infection, such as a bad tooth and washings of the sinuses.

He went along very well until April 29, 1932. His blood count was unchanged (table 1), and there were no symptoms resulting from his polycythemia. All this time he was receiving roentgen-ray treatment to his long bones, liver and spleen. During this period he developed pitting edema of his ankles and it was noted that there was a definite increase in the size of his heart after comparing the transverse diameter measurements with the previous ones.

On May 16, 1932, the following observations were made: The edema had increased, there were many moist râles at the lung bases and the liver was enlarged and tender. He was ordered to bed and treatment for congestive heart failure was instituted. From this point on his course was progressively downward; he gradually developed generalized anasarca. The response to mercurial diuretics was not satisfactory and he developed a toxic diarrhea from the mercury. On July 19, he developed a unilateral eruption (herpes zoster) over his lower back which gradually became generalized in distribution and hemorrhagic in nature. His terminal symptoms were uremic; there were muscular twitchings and delirium. The non-protein nitrogen of the blood was found to be 70 mg. per cent. The urine sediment contained many hyaline and a few finely granular casts and white blood cells. On July 27, he went into coma and died on July 28, 1932.

Autopsy Findings

There was marked edema of the soft tissues of the back and flanks. There was considerable pitting edema of the lower extremities and of the fore-arms and hands. The pleural cavities were free of adhesions and each contained about 1500 c.c. of clear amber fluid. The lungs were edematous. The heart weighed 450 grams. Both the left and right coronary arteries traced through their finer ramifications showed widely patent lumina. The vessel walls were free of any change and cross-sections of the finer twigs showed no visible occlusion anywhere. The intima of the aorta showed only small superficial yellow streaks of early atherosclerosis.

The peritoneal surfaces were glistening; the cavity contained about 1500 c.c. of dark fluid. The mucous membranes of the proximal ileum and of the jejunum were intensely red and contained light red fluid. Careful search for mucous membrane lesions or serosal induration was unsuccessful. The colon in its proximal half contained a small amount of yellowish fecal material; the distal half was empty. Similar search of residual or recent mucous membrane or serosal lesions was likewise

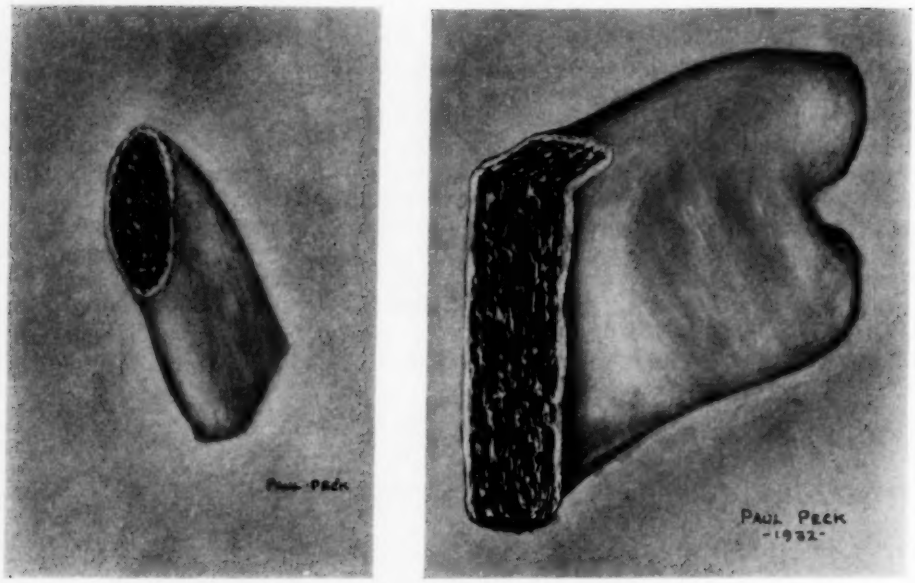
without success. The mucosa was intensely red, for the most part, and the serosa everywhere glistening.

The liver weighed 1500 grams and on section showed early "nutmeg" appearance. There were no abscesses. The surface was smooth and not thickened. The spleen was in a vertical position in the lateral aspect of the abdominal cavity. Its lower border was about 4 inches below the costal margin. The weight of the organ was 740 grams. There was a prominent notch in the normal position along the mesial border. On the upper surface there was a large irregular area of capsular wrinkling and thickening of a light brown color in contrast to the purple splenic capsule. There was a smaller area of similar capsular thickening and wrinkling at the medial anterior surface. Section of the spleen showed a firm, intensely red parenchyma, without any oozing of blood, homogeneous and without visible lymphoid follicles. Beneath the areas of capsular thickenings the parenchyma was lighter in color and indurated so that it was demarcated from the rest of the pulp and visible as circumscribed areas, each about 2 inches in diameter (figure 1). There was no

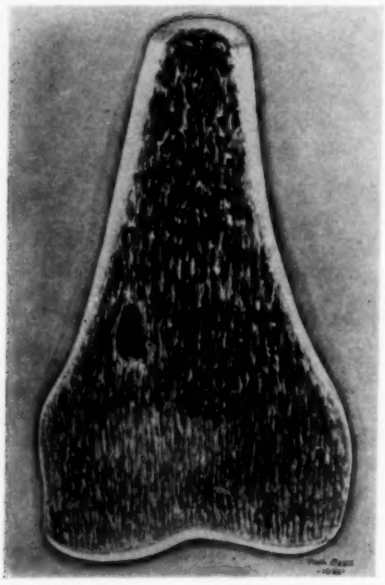
FIG. 1. The spleen was enlarged and firm. On section the parenchyma was deep red and homogeneous except for two circumscribed areas, lighter in color, situated beneath corresponding areas of capsular wrinkling and thickening.

accessory spleen. The splenic vein was followed from the hilus into the portal vein and the mesenteric veins were opened. All of these vessels were free from disease and thrombi. The splenic artery was entirely normal; its lumen was unusually large for this vessel and showed no arteriosclerosis. There were no enlarged peri-portal nodes. The kidneys were very unequal in size; the left weighed 450 grams, the right 30 grams. The capsule of the left kidney was free; its surface was diffusely, finely and coarsely granular, with a few small cysts containing clear fluid. The parenchyma was deep red and firm; the cortex was remarkably narrowed and irregular and its relations to the medulla were about one to three and one-half, measuring three to four mm. in width. The right kidney was similarly granular.

Bone Marrow: Cross-section of all the ribs which were examined showed abundant deep red marrow, with a thin cortex; the middle of the sternum was likewise distended with deep red soft marrow (figure 2). The entire marrow cavity of the lower end of the right femur was filled with deep red soft substance which occupied



a *b*



c

FIG. 2. Section of all the ribs (*a*) showed abundant, deep red marrow with a thin cortex. The sternum (*b*) was likewise distended with deep red soft marrow. The lower end of the right femur (*c*) showed a similar marrow. There was an increase in the bony trabeculations; the cortex was thinner than normal.

even the epiphyseal end of the bone down to the cortex of the articulating surface of the knee. The cortex of the bone appeared normal except for perhaps slight thinning. There was an increase in the bony trabeculations of the marrow (figure 2 c). The right knee joint was distended with about 150 c.c. of clear, thin yellow liquid.

Microscopically, sections of the spleen through the indurated areas beneath the region of capsular scarring showed a moderate thickening of the fibrous trabeculae of the pulp with propagated fibroblastic tissue extending out into the parenchyma so as to considerably diminish the size of the vascular spaces as compared with the less dense portions of the organ. The arterioles of the follicles were markedly thick walled and only in isolated instances showed any residuum of the normal lymphocytic mantle. The parenchyma appeared moderately cellular. With oil immersion magnification there was seen, in addition to the large endothelial cells lining the blood channels of the pulp, elongated reticulo-endothelial cells, and large and small accumulations of developing blood cells among which could be identified nucleated red cells, mature polymorphonuclear cells and immature large mononuclear white blood cells. These cells were in all instances interspersed with red blood cells so that it was difficult to decide the relationship of such blood cell islets to the vascular channels and pulp spaces. These cellular accumulations were, more often, particularly dense about the fibrous trabeculae. The striking difference seen in sections through the softer hemorrhagic portions of the organ was the more marked distention of the sinuses with closely packed red cells and far less interstitial fibroblastic tissue and relatively few white cells.

The kidneys in some areas showed widespread disease of the arterioles characterized by subendothelial fibroblastic proliferation often approaching and at times resulting in complete obliteration of the lumina. Almost all of the glomerular tufts in these areas showed changes, varying from a slight degree of peri-capsular fibrous thickening to marked encroachment on the substance of the glomerulus. Some were completely fibrotic; others had gone on to hyalinization. The large arteries were relatively normal.

Sections of bone marrow from rib, lower end of sternum and lower end of right femur showed essentially similar types and distribution of cells in each of these areas. The marrow of the rib appeared the least cellular, while that of the femur was the most richly cellular of the areas studied. Almost no residual fatty areas were found. The cellular elements, for the most part, could be separated into two major groups in nearly equal distribution as to numbers (figure 3). These represented the erythroblastic and myeloblastic series. In addition there was a generous number of scattered multinucleated giant cells, the megakaryocytes, as well as of the elongated cells of the reticulo-endothelium, and a large number of mature red blood cells. The normoblasts were identified by their small, round deeply staining nuclei with a pale cytoplasmic rim; many nuclei were in the process of budding, some were large with scalloped outline and others showed small satellite nuclei. The cells of the myeloblastic series were chiefly large, non-granular premature stem cells. The nuclei were granular, varied in size, at times occupied nearly all of the cell; in other instances smaller, with a rim of faintly pink staining cytoplasm. A considerable number of eosinophilic myelocytes could be easily identified. Only rarely was there seen a metamyelocyte or a segmented polynuclear cell.

Discussion

We did not consider the use of phenylhydrazine advisable in our patient because of his age; and the diseased kidneys discovered at autopsy justified our decision. The roentgen-ray therapy produced little improvement in his blood counts, although subjectively he was somewhat benefited. The

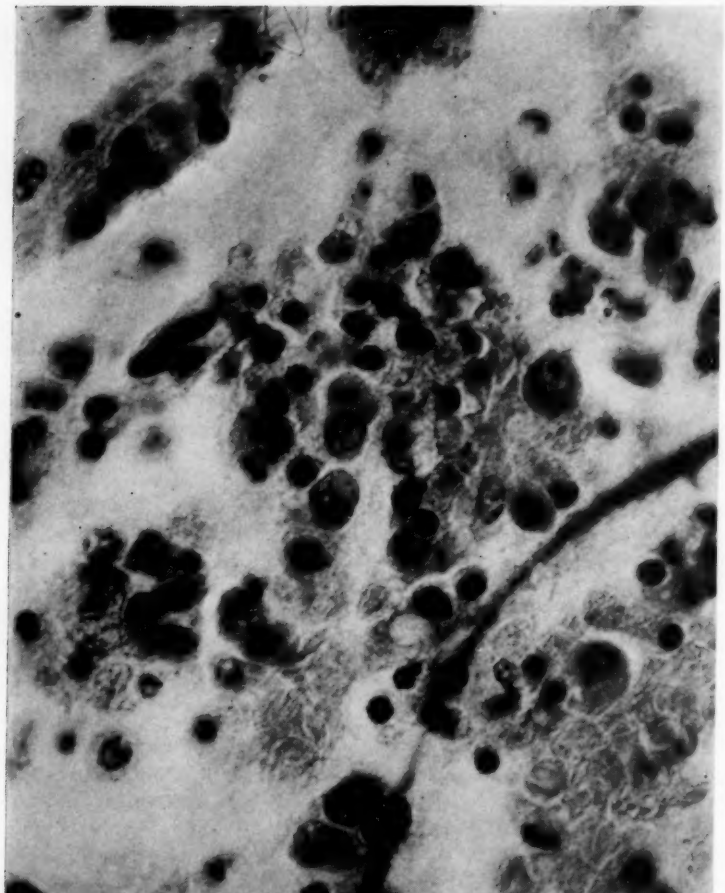


FIG. 3. Microscopic section of sternal marrow, Giemsa stain. The cellular elements represent the erythroblastic and myeloblastic series, in nearly equal distribution. The normoblasts are identified by their small, deeply staining nuclei with a pale cytoplasmic ring. Some are in process of budding, some have large nuclei with scalloped outlines, others show small satellite nuclei. There are a large number of mature red blood cells. The cells of the myeloblastic series are chiefly large, non-granular stem cells. A considerable number of eosinophilic myelocytes were identified. A generous, though not excessive, number of megakaryocytes were found; one is noted at the upper margin of the photograph.

colonic bleeding resulting from his amebiasis seemed to effect a distinct lowering of his red blood cell counts. Ordinarily, frequent venesections do not ameliorate this condition. The identification of the *Entameba histolytica* had been confirmed by a competent protozoölogist. The response to specific therapy was prompt. After death we had the unusual opportunity of examining the bowel of the patient cured of amebiasis. The complete absence of pathologic residua in such a case, both on gross and microscopic examination of the organs, is not a surprising finding according to experienced workers in this disease.[5]

The gross and histologic findings of generalized and active hematopoiesis did not impress us as having the morphology of a neoplasm of the blood-forming elements, as Minot [6] has suggested. There were no extramedullary foci of blood formation except for the myeloid alterations of the spleen. The lymph nodes were not enlarged. The microscopic sections showed all the normal elements of blood formation in equal and active regeneration. The bone marrow response was much as we see in active hematopoietic stimulation, not unlike that produced by bone marrow metastases of carcinoma of the prostate. In this case the stimulus remains unknown.

The hypercalcemia did not result in any unusual degree of atherosclerosis. The enlarged heart was evidently not necessarily due to the polycythemia since the nephrosclerosis with hypertension might equally well have been the cause. The heart showed no alteration except for hypertrophy. The coronary arteries, carefully examined, were not diseased. The precordial distress and the electrocardiographic changes must be ascribed to the hypertrophy of the myocardium. Death was apparently due to congestive heart failure with concomitant uremia. There were no terminal thromboses or hemorrhages, such as often cause death in erythremia. The use of salyrgan, indicated by the large accumulations of fluid and edema, probably hastened failure of the already markedly damaged kidneys.

The increased basal metabolism probably goes along with active regeneration of blood, such as we see in leukemia to a more marked degree. The blood was viscid and the proportion of red blood cells to blood plasma was markedly increased. The enlarged spleen was characteristic, except that it was more firm than is usual, probably the result of the roentgen-ray therapy, which may also account for the scarred areas in this organ. The splenomegaly was to some extent explained by the myeloid metaplasia, but for the most part was due to the great increase in blood content. We have seen a case where the enlarged spleen rapidly decreased in size just before death due to a fatal gastrointestinal hemorrhage, demonstrating the reason for the enlarged organ in that patient with polycythemia vera.

The nationality of our patient was American of English ancestry, therefore, not conforming to the majority of patients with erythremia who as Dr. Paul Reznikoff [7] has shown from the series he compiled, more usu-

ally come from Eastern Europe. This author also pointed out the presence of arteriosclerosis in the smaller arteries in the bone marrow sections of our case and considered it a finding of considerable significance. If these vascular changes were the cause of a relative anoxemia of the bone marrow this might be an etiologic factor of importance.

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THE TREATMENT OF LOBAR PNEUMONIA BY ARTIFICIAL PNEUMOTHORAX

A STUDY OF TWENTY-FIVE CASES *

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THE correct appraisal of a new therapeutic measure is always difficult and in a disease presenting as many variables as pneumonia, it is particularly so. Not only does the mortality vary in different years but it is influenced by the age of the patient, the type of pneumococcus, the presence of complications and especially by the duration of the disease before the treatment is begun. Accordingly, no final opinion as to the value of any treatment can be arrived at until a large group of treated cases is compared with a similar untreated group. Our series is so small that no definite conclusions can be drawn; we merely present our observations together with certain impressions we have received.

While a number of clinicians in several widely separated parts of the world had reported successful results with this treatment,[1] it was not until the work of Lieberman and Leopold,[2] who treated experimental pneumonia by pneumothorax, that a real interest in the procedure developed. Of the 18 dogs in their series not given treatment, 13 died; of the 18 treated, three died. They were able to find only 50 human cases reported—the ages varying from six weeks to 62 years. In some of these the benefits of the treatment were not especially convincing though the relief of pain was noted by all. Since their paper, 11 cases have been reported by Behrend and Cowper,[3] and Blake [4] had also reported a group of 24 cases.

RATIONALE OF TREATMENT

Before proceeding to review our results or to discuss certain controversial points, let us consider the rationale of the procedure.

When one thinks of the pathology of lobar pneumonia he is apt to visualize the consolidated lung as seen at autopsy five or more days after the onset; and the futility of trying to collapse or even compress so solid an organ is very apparent. This, however, is a terminal stage and is as different from the condition present during the first few hours after onset as the ruptured, gangrenous appendix differs from the slightly injected organ that characterizes the early stage of this disease.

Terrell, Robertson and Coggeshall [5] produced experimental lobar pneu-

* Received for publication April 17, 1935.
From the Medical and Roentgenological Services of Hartford Hospital.

monia in dogs by introducing virulent culture into a terminal bronchus. They found that the earliest and most striking finding was extensive perivascular edema. Many of the alveoli also were filled with fluid. While these changes were evident as early as the first hour, they were not marked until the sixth hour; and by the twelfth hour the greater part of the lobe was consolidated and fibrin was beginning to form on the pleura. The most recently involved part (the periphery) was the most moist; the central or older part, less so; and an observation of the greatest significance was that pneumococci were most numerous in the periphery of the lesion, i.e. where the edema was greatest.

Inasmuch as Rhoads and Goodner [6] believe that edema fluid is the principal agent in the dispersion of pneumococci, any measure that has as its object the mechanical limitation and dissipation of the congestion and edema, must be given attention. According to Lloyd,[12] by increasing the intrapleural pressure in a pneumothorax, the lymph flow may be reduced by as much as 50 per cent.

In studying the blood flow through the lungs after experimental pneumothorax in rabbits, Dock and Harrison [7] found that even though they employed slightly positive pressure, complete atelectasis of the collapsed lung did not occur at once. Only when positive pressure was maintained for from three to five days did a complete atelectasis result. They concluded that the therapeutic value of artificial pneumothorax must be ascribed to ischemia.

Fifty years ago when Foralini began to treat tuberculosis with pneumothorax, he felt that a complete collapse of the whole lung was desirable. As experience accumulated, it became evident that this extreme measure had very definite disadvantages, and finally the idea of partial or selective compression found acceptance among phthisiotherapists. Selective collapse is in effect "an automatic mechanism, the resultant action of the simultaneous tendency of the diseased part to collapse and of the healthy part to expand." [8]

The act of coughing suddenly raises the intrapleural pressure and a mean pressure that on quiet breathing is zero, or even slightly negative, will suddenly become strongly positive with sharp cough. For this reason, during the pneumothorax treatment of pneumonia, complete abolition of cough is perhaps undesirable. Lobar pneumonia and subacute, or chronic tuberculosis, differ so much in their pathology and course that the rather leisurely compression of the tuberculous lung generally practiced would not be applicable to the more acute disease.

Can one secure selective compression or collapse of a lung which is the site of a beginning pneumonia? This is hard to determine because the patient, as a rule, is so ill that it is difficult to obtain satisfactory serial roentgen-ray films. We were fortunate, however, in having an early patient who, because he did not seem very ill, was given only one injection of 250 c.c. about 30 hours after the onset, for the relief of pain. Figure 1 shows

the lesion at the right base on admission. Figure 2, which was taken about 20 hours after the air injection, shows the lung to be adherent in the lower axillary region but separated from the diaphragm elsewhere by air. There is also a small amount of air at the apex. Most of the air, as the lateral view showed, lay between the lesion and the anterior chest wall. The chief interest, however, is the fact that the pneumonic area shows considerable clearing due presumably to the lessening of the edema and congestion as the result of the selective collapse. Furthermore, the immediate relief of pain that so often follows the injection of a very small amount

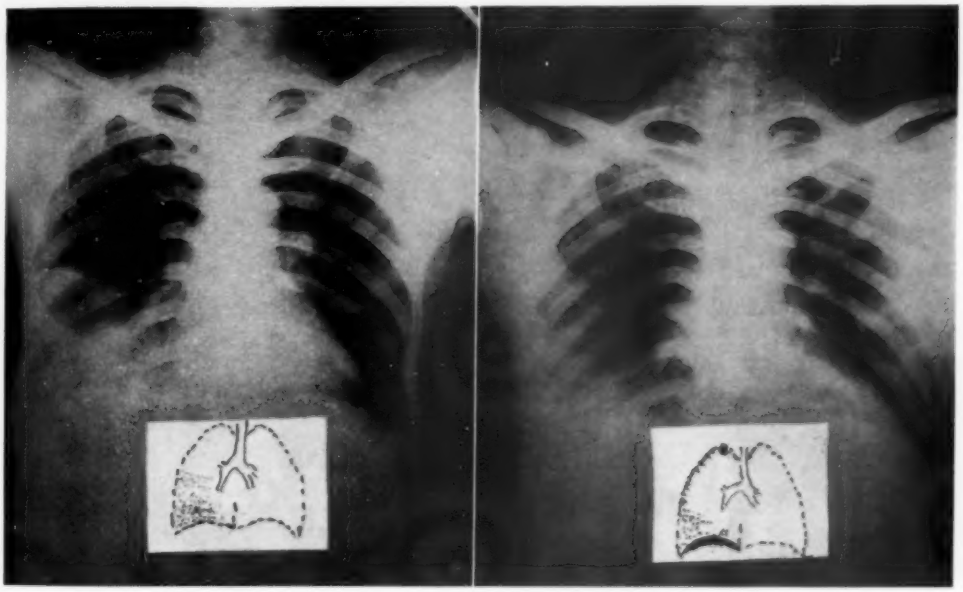

FIG. 1. FIG. 2.

Selective collapse following single injection of air in early lobar pneumonia.

FIG. 1. Right lower lobe, second day of disease before treatment.
FIG. 2. After injection of 250 c.c. air. Small amount of air at extreme apex; slight separation of lower lobe from diaphragm by air. (In the lateral view considerable air was seen anteriorly.) Note especially that the right lower lobe is much better aerated due presumably to less congestion and edema. (In the diagrams accompanying roentgen-rays, normal lung is left blank, pneumonic areas are dotted and pneumothorax is entirely black.)

of air (50 to 100 c.c.) can be accomplished, obviously, only by compressing the lung at the site of the lesion.

Autopsy proof that a small amount of air can cause a selective compression of a lobe, the site of an influenzal pneumonia, was furnished in 1918 by Rood [9] while doing lung punctures on a number of patients ill with influenzal pneumonia to determine if possible the infecting organism. A few developed pneumothorax as a result. As they seemed to be much improved when this occurred, he injected three apparently moribund pa-

tients with from 100 to 150 c.c. of air. Two recovered and the third showed striking improvement but relapsed and died. At the autopsy, the lower lobe the site of the pneumonia, was compressed to one-third of its normal size and did not contain the usual amount of exudate, while the upper lobe, which was not hemorrhagic, showed but little compression. It is of interest that such a small amount of air was able to produce so marked a selective collapse of the pneumonic lobe.

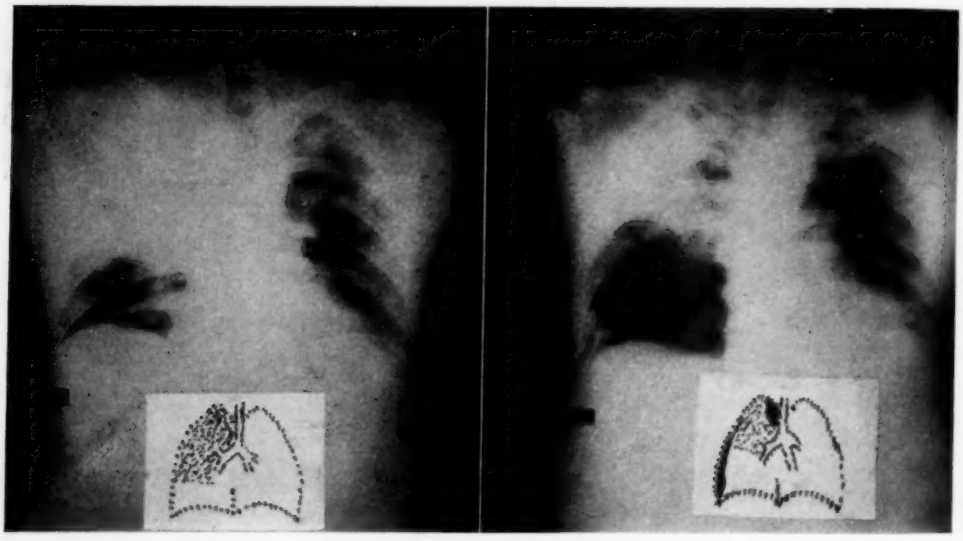

FIG. 3. FIG. 4.

FIG. 3. Consolidation right upper, third day.
FIG. 4. After 650 c.c. of air.

ANALYSIS OF CASES

At the beginning of our investigation it was appreciated that if only such patients were treated as had not been ill over three days, and if the elderly cases with complications were excluded, a much lower mortality would be obtained. Such a selection should be made if a control group of non-treated cases could be run at the same time. As this was not possible with the material available, it was decided to treat all cases as they came in. This was done with the exception that two very mild cases were not given injections as we felt they would recover without any treatment. No case was admitted in extremis. All patients on admission had a blood culture, a leukocyte count and a bedside roentgen-ray (both postero-anterior and lateral). The treatments were followed by frequent roentgen-rays; from 10 to 15 being taken in many cases. This work was under the supervision of Dr. Ralph T. Ogden.

Of the 25 patients, seven died—a mortality of 28 per cent. Felton's

antipneumonic serum was administered to three who died and to an equal number of those who recovered. In two of the fatal cases it was used too late to be of value.

Fatal Cases. In the main, the fatal cases (table 1) were elderly indi-

TABLE I*

Fatal Cases

H. H. Number	Age Sex	Type Site	Day Dis.	Bld. Cult.	No. Treat. Total Amt.	Relief Pain	Prompt Detoxification	Day Death	Day Serum Given	Complications Comments
287680 S. I.	69 M.	II R.u.	4	+	5 1500 c.c.	No	No	7	No	Adhesions +3 Severe asthma
287737 O. W.	75 F.	I R.l.	2	+	6 2125 c.c.	No	No	4	3 30,000 units	Adhesions +3 Severe asthma Empyema (Pneumo.)
287796 F. P.	53 M.	I L.l. R.u.m.	5	+	2 1250 c.c.	Pain incr. adh.	No	7	6 51,000 units	Auric. fibril. Arteriosclerosis Adhesions +3 (N.P.N. 89) Serous effusion
289058 A. W.	85 F.	III R.u.	4	+	3 475 c.c.	+3	No	5	No	Coronary thrombosis
288023 F. S.	50 M.	IV R.u.m.	3	+	3 1850 c.c.	+3	2	7	No	Diabetes—Peritonitis (?) Large intest. hemorrhage
288583 C. F.	30 M.	I L.l.	3	−	4 800 c.c.	+1	2	14	6 90,000 units	Adhesions +3 Empyema (Pneumo.) Peritonitis; intest. obstr. (*B. coli;* few non-hemolytic strep.)
287482 J. A.	71 F.	III L.l. R.u.m.	6(?)*	−	12 5L. 900 c.c. 7R 1625 c.c.	−	No	13	No	Adhesions +2 Nephritis (N.P.N. 150)

* Estimating the day of disease when pneumonia follows a "cold" is often very difficult. History frequently suggests an older lesion than physical signs or roentgen-rays indicate.

In tables 1, 2 and 3 R. is right lung
L. " left lung
u. " upper lobe
m. " middle lobe
l. " lower lobe.

In the tables, the degree of relief of pain and detoxication is expressed numerically, *3* indicating marked, *2* and *1* less so.

Adhesions *4*. No pleural space.
3. Preventing collapse of pneumonic area.
2 and *1*. Strings or bands that allow some compression of the involved lobe.

viduals with a variety of severe complications who had been ill several days when treated. Extensive adhesions prevented satisfactory compression of the lung in practically all cases. The average age of the fatal group was 62 years. Only one was under 50, three were over 70 and one 85. Of those who recovered, the average age was 25 years. The patients who died had been ill on an average of 3.8 days when treated, those who recov-

TABLE II

No. cases	Age	Deaths
5	under 20 yrs.	None
7	20–39 "	1
8	40–59 "	2
5	over 60 "	4

ered, 2.3 days. Thirteen were treated within 48 hours after the onset with one death. This patient showed initial improvement but developed empyema, peritonitis and intestinal obstruction. The seriousness of the disease in the older age groups is shown in our series.

Positive blood cultures were present in five of the seven fatal cases but in none of those which recovered, though in several more than one culture was taken. Of equal if not more importance in determining the fatal outcome were the complications that were not directly related to the pneumonia. Two had very severe spasmodic asthma, one intestinal obstruction due to general peritonitis, one, a diabetic with paralytic ileus, had a large intestinal hemorrhage, and one died of coronary occlusion. A prompt but temporary detoxication followed the institution of treatments in two of the cases, but in each complications proved fatal.

Recovered Cases. Eighteen patients recovered (table 3) but what part the treatment played in any individual case is difficult to say, for who has not seen the utterly hopeless case recover without any special treatment and the mildest case become suddenly fulminating? Yet those of us who saw the cases most intimately were of the opinion that when a successful compression could be obtained early, the patients were not only much more comfortable but seemed to be quite promptly detoxicated. In a number, the course of the disease seemed to be shortened. Yet in seven of the cases which recovered, it did not seem that one could attribute the recovery to the treatment as their course did not seem to be influenced by it. In some the treatments were too far apart. Two had been ill a long time when treated (six or seven days). One did not appear seriously ill and was given a single injection for the relief of pain but we felt he would have recovered without it.

As has been said, the most satisfactory results were obtained when the treatment was administered early and when adhesions were absent or did not interfere with compression. (Charts 1 and 2.)

The question of "aborting" pneumonia before there is radiographic evidence of the lesion is an intriguing one. Unfortunately at this time the physical signs are also indefinite. Some who saw one of our cases felt that pneumonia was probably aborted, though others were skeptical. (Chart 4.) We have seen the roentgen-ray films of a similar case in another hospital where treatment was not given on admission because of a lack of radiographic evidence. Films taken a few hours later, however, demonstrated the lesion. The roentgen-ray may show an apparent increase in the amount, or degree, of consolidation when the patient clinically shows great improvement. This sometimes occurs following the use of specific serum.

Six of our cases had bilateral involvement (24 per cent) and two of these died (35 per cent). Five of the six received bilateral injections with one death (20 per cent). Two of these, however, also received type serum

TABLE III

Recovered Cases

H. H. Number	Age Sex	Type Site	Day Dis.	Bld. Cult.	No. Treat. Total Amt.	Relief Pain	Prompt Detoxification	Day Dis. Temp. 100	Day Serum Given	Complications Comments
287435 M. F.	22 F.	IV L.l.	6	—	3 700 c.c.	?	?	10	No	Adhesions +2 Time onset? Following influenza Annoying cough not relieved by treatment
286098 J. H.	41 M.	IV R.l.	2	—	1 250 c.c.	+3	never toxic	never higher	No	Very mild case Definite onset; chill; bloody sputum but not toxic
287055 L. S.	44 M.	III R.u.	3	—	2 650 c.c.	+2	+3	4 Chart I	No	Adhesions +1
285304 J. B.	24 M.	IV R.u.	3	—	4 970 c.c.		+3	7	No	
287171 F. M.	16 M.	IV R.l.	2 (42 hrs.)	—	5 1700 c.c.	+3	+3 Chart	4	No	
287659 E. C.	54 F.	Not determ. R.l.	2	—	5 2300 c.c.	+3	+3	4	No	
287989 R. R.	17 F.	I L.l. R.m.	2	—	4 2L. 900 c.c. 2R. 500 c.c.	+3	+3	4	3 90,000 units	Adhesions +2 Bilat. involvement Serum given after spread
291860 A. S.	40 M.	II L.l.	1 (23 hrs.)	—	7 6L. 2650 c.c. 1R. 200 c.c.	+2	—	4	3 100,000 units	Adhesions +2 Serum given after spread
288501 J. B.	68 M.	I L.l.	5 chart 8	—	5 1600 c.c.	+1	+3	9	No	Adhesions +2
288555 G. D.	46 M.	II L.l.	2	—	5 1900 c.c.	+1	+3	6	No	Adhesions +2
288108 W. B.	14 M.	II L.l.	1 (13 hrs.)	—	11 6L. 2100 c.c. 5R. 1800 c.c. Decompressed 1600 on L.	?*	+1	5	No	Adhesions +2 Spont. pneumothorax? Congent. heart disease Bilat. involvement
288608 H. G.	38 M.	II L.l.	1 (15 hrs.)	—	4 1550 c.c.	No	No	13	2 and 3 90,000 units	Adhesions +2 Air treatment; no result. Small Plv. effus.
288312 J. L.	13 M.	IV R.l. m.	7 *see text	—	6 1130 c.c.	No	No	13	No	Adhesions +3 Pt. treated seventh day after onset of lesion lower right lobe and 24 hrs. after spread to right upper
287443 A. C.	33 M.	IV R.u.	2	—	3 1300 c.c.	No	+2	3 ChartII	No	
289122 D. H.	55 F.	III L.l. R.l.	2 (30 hrs.)	—	7 4L. 375 c.c. 3R. 450 c.c.	No	+1	6	No	Adhesions +3 Pt. wildly delirious
289363 A. M.	28 M.	IV L.l.	2 (29 hrs.)	—	7 2025 c.c.	+3	+3	3	No	
289431 R. C.	38 M.	IV R.l. m.	3	—	6 1700 c.c.	No	No	8	No	Adhesions +3 Course unmodified
290000 A. K.	16 M.	I R.l.	2 (26 hrs.)	—	8 2300 c.c.	+2	+2	7	No	Adhesions +2 Detox. followed treatments but never complete

* Due to low I.Q. of patient difficult to determine.

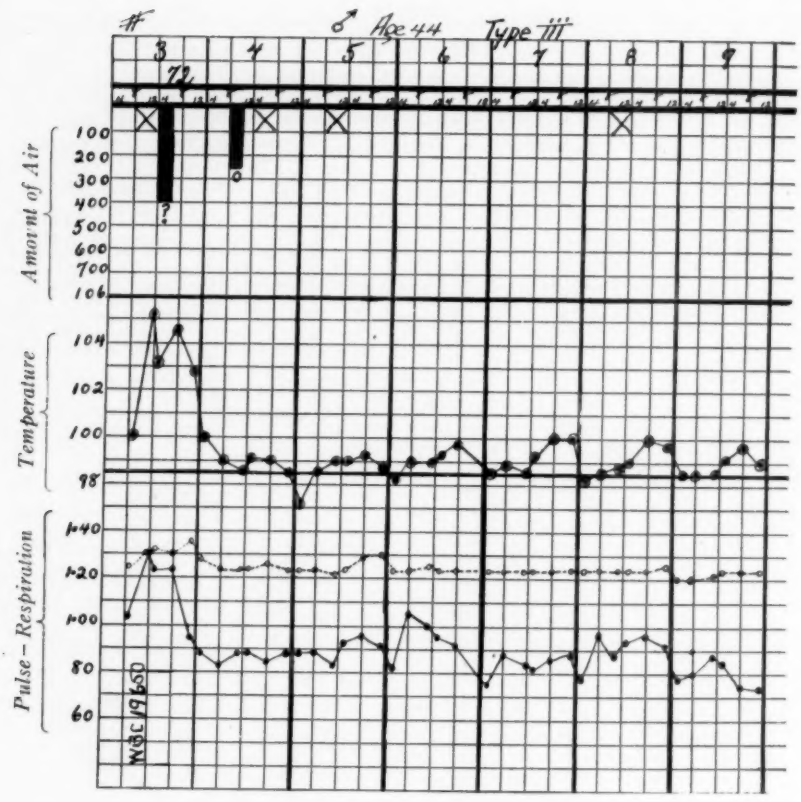

CHART I

L.S., male, age 44; type 3, R.u.; third day of disease; W.B.C. 19,650 82/18; blood culture negative. He was given 400 c.c. shortly after admission. A profuse sweat followed with complete detoxication. The next morning, though he appeared well, he was given another injection of 250 c.c. At the conclusion of both treatments the mean intrapleural pressure was slightly negative.

Especial attention is drawn to the fact that he received an injection after the temperature was normal and he seemed well. We did not at this time appreciate the importance of this extra treatment.

when the spread to the contralateral lung took place. These will be reported separately.

DISCUSSION

Frequency of Treatment. As the result of many years of experience in treating tuberculosis with pneumothorax, our early cases were given moderate amounts with a negative mean pressure at the conclusion. The interval between treatments in the early cases was about 12 hours. Several of the patients so treated appeared to be benefited. In some the pressure was zero (atmospheric) but in all of these, as has been said, the pressure would become positive with each cough. In a few the final mean pressure was plus two or three cm. of water. As the lymph stasis and the

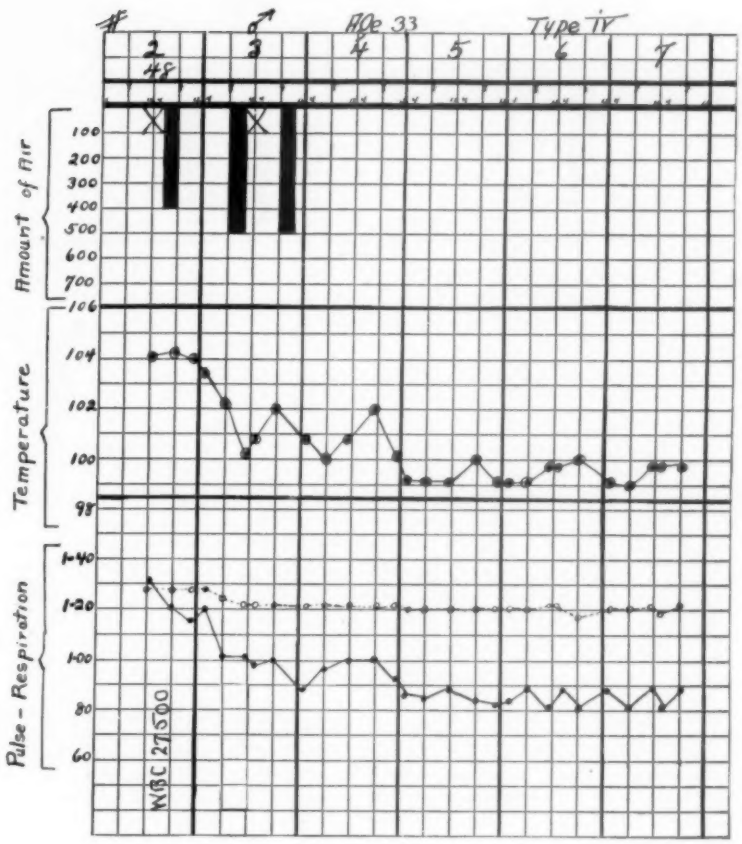

CHART II

A.C., male, age 33; type 4; second day (48 hrs.); W.B.C. 27,500 82/18; blood culture negative. He appeared to be a moderately severe case. He was given 1400 c.c. in three injections. Following the first there was a marked drop in temperature and pulse. The next two treatments were given at just the right time before the temperature rose, i.e. before the lung expanded. He appeared to have no adhesions.

diminished blood flow in the collapsed lung result in a decrease in circulating toxins, the first three or four treatments should be given at intervals of four to six hours. *It is particularly important when clinical improvement follows and the temperature falls to normal, to give another injection promptly* because with the slight expansion of the lung, the temperature is apt to rise and the toxemia to reappear. This is well shown by charts 1 and 4.

The Optimum Pressure. Of all who have employed this treatment in pneumonia, Blake alone advocates complete collapse of the whole lung as promptly as possible, maintaining this during the first 24 to 48 hours by frequent refills. He employs large amounts of air and aims to keep the mean intrapleural pressure positive at all times. Analysis of his cases

CHART III

R.C., male, age 38; type 4; third day; R.I. and m.; W.B.C. 20,600; blood culture negative. Vague history of ill-health. The house officer thought he had a pleural effusion, so no injection was given on admission. The next morning he had bronchial breathing over the right lower lobe but there was also an area of bronchial breathing near the lower angle of the left scapula. Fearing a possible bilateral process, we postponed the treatment several hours until another roentgen-ray film showed the left lung to be clear at which time 400 c.c. were injected. Five and one-half hours later 550 c.c.; seven hours 100 c.c.; 11 hours no injection as the mean intrapleural pressure was plus 1 c.c.; 16 hours 400 c.c.; 16 hours 50 c.c. The pressure was slightly positive at end of each treatment but the patient never perspired and his pain was not relieved. The roentgen-ray showed the lung to be adherent to the diaphragm.

When we find we can introduce only a small amount of air after several hours (in this case 50 c.c. after 16 hours) in a patient who has readily taken larger amounts, we have found that serum has formed. In this case 70 c.c. sterile serum were aspirated. The temperature fell gradually as one would expect in the untreated case. Three times readings of intrapleural pressure were taken but no air injected as pressure was positive (♂).

appears to show that the cases so treated received the greatest benefit. All the others who have used this treatment endeavored to compress the lung rather than to collapse it and have kept the intrapleural pressure slightly negative or neutral.

We seriously question the wisdom of employing large amounts (800 to 1000 c.c.) in patients exhibiting evidence of marked arteriosclerosis as it seems possible that a change in blood flow through the sclerotic vessels might occur as the result of the mediastinal shift and serious results follow. On the other hand, it may require slightly positive pressure at the first few treatments to secure adequate compression and to separate the freshly adherent pleural surfaces.

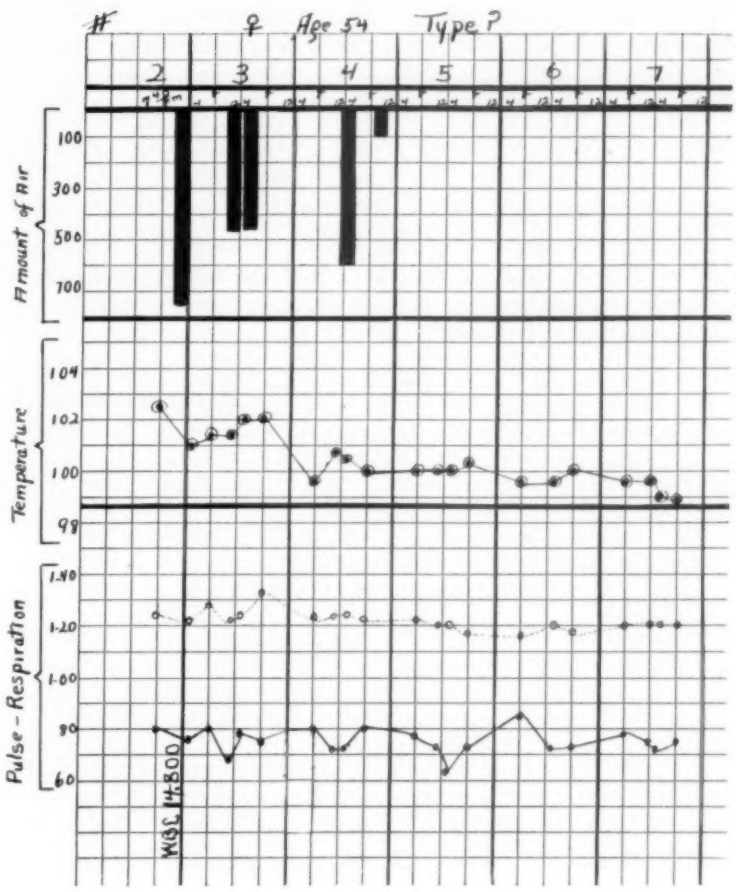

CHART IV

E.C., female, age 58; type not determined; R.I. ?; onset 24 hours or less; W.B.C. 14,800 83/17; blood culture negative. A month prior to present illness patient had a cold of several weeks' duration with pain in right lower chest and a chill that was repeated shortly before admission: also the day before admission she began to cough, with greenish expectoration. She appeared moderately toxic. There was diminished expansion due to pain in right side, and a questionable dullness and a few fine râles were heard over the lower lobe.

She was given five injections, the first of 750 c.c., and 2300 c.c. in all were given. The pressure was slightly positive after the last two treatments; the others slightly negative. Pain was greatly relieved and the toxic symptoms promptly subsided.

Roentgen-rays on admission: "No definite evidence of pneumonic consolidation. The peribronchial structure extending into the basal portion of the right lobe posteriorly towards the mediastinum is exaggerated. The heart appears retracted slightly to this side and the right diaphragm is slightly elevated. These findings are compatible with the congestion of a beginning pneumonic type of process or partial atelectasis of the lower lobe."

When large amounts of air have been injected with resultant shift of the mediastinum, we have frequently noted some increase in the peribronchial markings in the roentgen-ray film and a few times a general haziness of a considerable part of the contralateral lung, which promptly

subsided following decompression. We suspect this to be due to some interference with the lymph and vascular circulation rather than to atelectasis. In one case (W.B.) whose several injections were given on both sides because of a spread a spontaneous pneumothorax apparently developed. Several hundred cubic centimeters of air were aspirated. The patient recovered.

A change in the position of the trachea is the best indication of mediastinal shift. Several years ago, Webb, Forester and Gilbert [11] described a simple and very accurate clinical method of determining its position. Their technic has proved of great value in our cases and on the whole it is as accurate as the roentgen-ray.

Pleural Effusions. How frequently lobar pneumonia is accompanied by the collection of serum in the pleural cavity is unknown. None of Lieberman and Leopold's dogs that died had any pleural effusion. The roentgen-ray evidence of small amounts (100 c.c. or less) is not conclusive though we have learned to regard a slight ground-glass appearance as suspicious. Following air injections when films are taken in the upright and lateral positions, very small amounts can be identified.

Serum was present in 15 of our cases, usually in small amounts. The maximum amount was 700 c.c. Whether the frequency of its occurrence and the amount depend upon the pressure used is not known. It would seem as if its incidence might be increased by positive pressure. The temperature of the air introduced may also be a factor. When after an interval of several hours following an injection of several hundred c.c. of air, the intrapleural pressure has not fallen or has become positive, serum has probably begun to form. Pneumococcus empyema developed in three cases with two deaths: one of these two had peritonitis and intestinal obstruction, and the other patient, aged 75, had severe asthma. In the third case, several unsuccessful attempts were made to locate a small encapsulated empyema and once, when zeal exceeded judgment, the needle was introduced too low, as the subsequent roentgen-ray showed a small amount of air below the diaphragm. There were no untoward symptoms and the air was promptly absorbed.

Adhesions. Evidence has been presented in the case reports that the most serious obstacle to this form of treatment is adhesions. Even patients who recall no previous pulmonary disease are often found to have them. They were present in 19 of our 25 cases and in 13 of those who recovered. Our earliest case, treated 15 hours after the chill, had such extensive adhesions that the pneumonic site could not be compressed. When the relief of pain during a treatment is followed by a pulling sensation, referred usually to a different area, the presence of an adhesion is suggested. Adhesions are especially difficult to combat when present over the lower lobes. The lung that is stuck fast to the diaphragm is the most serious obstacle to this treatment.

The earlier the treatments are started the easier it is to separate the pleural surfaces. When a string type of adhesion is met with, one should always realize the possibility of a spontaneous pneumothorax if positive pressure is used. If adhesions are extensive and do not appear to be giving way after three treatments and the patient has not shown definite clinical improvement, further injections will probably prove unavailing.

Summary

1. The pneumothorax treatment of pneumonia is safe when properly carried out but experience in pneumothorax technic is a prerequisite.

2. Pleural adhesions are very common, especially in the elderly, but unless extensive, a satisfactory result can often be obtained unless their location prevents compression of the site of the lesion. In our series they prevented an entirely satisfactory compression in nearly 30 per cent of the cases. When the lower lobe is involved and adherent to the diaphragm, the results are unsatisfactory.

3. If adhesions are not present, pain is at once relieved, respiration is deeper and sleep follows, sometimes during the treatment. Morphine is not needed and only an occasional dose of codeine is required.

4. Cases adequately treated within the first three days will usually show complete detoxication with fall of temperature and profuse sweating within 12 hours, though the temperature may not remain down until a day or two later. Treatment is of little value after the third day.

5. The first three treatments should be given at intervals of four to six hours and it is advisable to give one more treatment when the temperature reaches normal even though the patient may appear to have completely recovered.

Conclusions

When compression can be effected early and maintained, pain is relieved and a prompt lessening of the toxemia is to be expected. It is probably the best treatment for the types for which there is no anti-serum. Due to the frequency with which adhesions occur, it cannot supplant the use of serum in suitable cases (Types I and II). However, not infrequently one may secure the benefits of a satisfactory compression before the type has been determined.

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THE OCCURRENCE OF CORONARY AIR EMBOLISM IN ARTIFICIAL PNEUMOTHORAX*

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ALTHOUGH air embolism is an infrequent complication of diagnostic and therapeutic measures, it is so startling and dramatic in its manifestations as to have been long a subject of great interest. Its occurrence has not been limited to any one field of medicine. Otolaryngologists have reported cases following antrum puncture (Garding,[1] Bacher[2]). Gynecologists have observed the condition in induced abortion, and also in version in cases of placenta praevia (Fink,[3] Gough[4]). In the field of general surgery it has apparently been most common in operations on the neck. This is probably due to the size of the venous channels in this region. Chest surgeons and those employing pneumothorax therapy, however, have encountered this complication more frequently than any other group. The reason for its more frequent occurrence in operative procedures involving the lungs as compared with those dealing with other organs is readily understood. Large quantities of air can be injected slowly into the systemic veins without harm (Schlaepfer,[5] Jackson and Babcock,[6] Bergstrand,[7] Joannides and Tsoulos[8]). On the other hand, as little as 0.5 to 1.0 c.c. of air in the left heart or carotid artery (comparable for practical purposes to air introduced originally into the pulmonary veins) may be fatal, as shown experimentally by Schlaepfer,[5] Stepp and Parade,[9] and others.

The clinical picture observed in cases of air embolism due to the introduction of air into the pulmonary veins is variable. In most cases the patient complains first of giddiness or faintness, and then lapses suddenly into unconsciousness with convulsions, which may be generalized or Jacksonian in type. The pupils are dilated and there is often conjugate deviation of the eyes. Circulatory collapse is a prominent feature. Death may follow or there may be gradual recovery. In non-fatal cases monoplegia or hemiplegia may persist for a variable period of time. Transient blindness or aphasia is relatively common. Air bubbles have been observed passing through the retinal vessels (Wever[10]). Neurological findings are not always present, however, some cases being characterized by unconsciousness and circulatory collapse only.

In the past the clinical picture just described has been widely attributed to "pleural shock" or "pleural eclampsia"; a condition supposedly of reflex origin. That irritation of the inflamed visceral pleura by various means does in some cases produce vago-inhibitory phenomena, and in others vasomotor disturbances, has been conclusively demonstrated by Capps and

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Lewis.[11] Their experiments failed, however, to reproduce a picture identical with that observed clinically. In their experiments no neurological signs suggesting focal lesions in the central nervous system occurred. On the other hand, Wever,[10] Schlaepfer,[12] Rukstinat,[13] and others have shown that the injection of air into the carotid artery or left ventricle in animals produced signs and symptoms similar in every respect to those seen in patients. At the present time phthisiologists and chest surgeons are generally in accord with the view that pleural reflexes may account for some of the less serious accidents complicating artificial pneumothorax and other thoracic operations, but that those cases presenting features of the severity described above are due to air embolism.

Artificial pneumothorax is the procedure most frequently complicated by air embolism. In most cases it is the attempt to induce pneumothorax, or the attempt to reclaim a lost pneumothorax pocket that results in the wounding of a pulmonary vein with consequent air embolism. However, in cases with an established pneumothorax the needle may enter a vessel in an adhesion with the same result. It is to be emphasized that many cases have occurred in which no air has been injected. There is sufficient air in the tubing of the pneumothorax apparatus to cause serious embolism if it is sucked into a pulmonary vessel. This fact led Cobbs[14] to suggest that, in inducing a pneumothorax, the needle be introduced with the bottles of the pneumothorax apparatus so adjusted that there would be a negative pressure of 4 to 5 cm. of water in the tubing. This maneuver does not prevent air entering a wounded vein by means of a broncho-venous fistula, should such an injury be produced by the needle, but is distinctly of value in giving a certain degree of protection.

Estimates as to the frequency of air embolism as a complication of artificial pneumothorax vary considerably. Probably a fair estimate would be about once in every 2000 to 3000 refills. One might expect the condition to occur more frequently, but it is probably true that an injured vein will not, in most instances, permit the entrance of air unless it is held open by indurated lung tissue (Schlaepfer).

Throughout the literature dealing with the clinical picture in air embolism, emphasis has been placed on the obstruction of the cerebral vessels as the important factor in the causation of death. Recent studies, however, indicate that air in the coronary arteries plays a very important rôle in the fatal outcome. Rukstinat and LeCount's[15] experiments are of particular interest. Working with guinea pigs, these investigators produced broncho-venous fistulae by raising the intra-tracheal pressure sufficiently high to rupture alveoli into adjacent blood vessels. Convulsions were invariably produced when the pressure was raised to 30 mm. of mercury. A pressure of 45 mm. of mercury always resulted in death in 50 to 75 seconds. Necropsy, carried out under water, revealed air in the coronary arteries in all the animals. There was a 50 to 90 per cent filling of the coronary channels with air. Hemorrhages in the myocardium were noted in some instances.

More recently Rukstinat [13] has published the results of further studies on coronary air embolism, using the dog as the experimental animal. In these experiments the rapid injection of air into the coronary arteries was immediately followed by tumultuous heart action, and acceleration which gave place within 10 to 20 seconds to pronounced slowing of the heart rate. Death occurred in one to four minutes. Air injected slowly in amounts up to 20 c.c. caused only temporary cardiac disturbances. No statement is made as to whether or not infarcts developed in any of the animals which recovered, and no electrocardiographic studies were carried out. Air injected into the left auricle caused death from coronary air embolism in 35 to 70 seconds. Left auricular injections were likewise fatal in a group of animals in which the carotid and vertebral arteries had been ligated 15 minutes previously, in order to eliminate cerebral embolism as a factor in the fatal outcome. Rukstinat concludes from his experiments that obstruction of the coronary arteries must be considered of great importance in all cases of air embolism originating in the pulmonary circulation.

A search of the literature reveals only one experimental study dealing with electrocardiographic changes in air embolism. Stratman and Uhlenbruck,[16] using the dog as the experimental animal, took electrocardiographic tracings following the injection of air into the femoral vein. Various disturbances of rhythm, and changes in the form of the P, QRS, and T-deflections, were noted. The striking feature of the tracings presented by these authors, however, is the presence in some of monophasic deflections of the type seen clinically and experimentally in the early stages of coronary occlusion. No statement is made, however, as to the presence or absence of air in the coronary arteries at necropsy. In one of the animals air had passed through the pulmonary capillaries in sufficient quantities to be found in the systemic arteries.

Clinical reports of coronary air embolism are few in number, possibly because the interest of the observer has been centered on the cerebral manifestations. Jackson and Babcock [6] report a case in which sudden death occurred during an open operation for empyema in a male, aged 23 years. There was systolic arrest of the heart. This, the authors believed, was due to coronary air embolism, although no statement is made as to the actual observation of air in the coronary arteries.

Pollak [17] reports a case in which the coronary vessels were filled with air at the time of the postmortem examination. The patient had developed a spontaneous pneumothorax, which was treated by the aspiration of air. One hour following the aspiration, the patient suddenly collapsed and became markedly cyanotic. Death ensued a few hours later.

The following case is of particular interest because electrocardiograms were taken both before and after the apparent occurrence of coronary air embolism during an attempt to produce artificial pneumothorax for the treatment of pulmonary tuberculosis.

Case Report

An unmarried woman, aged 24 years, was admitted to the Tuberculosis Unit of the University Hospital on July 28, 1932, with a history of four attacks of pleurisy during a period of five years. There had also been cough, productive of a moderate amount of purulent sputum, ease of fatigue, and loss of 12 pounds in weight. The patient had been told in 1931 that she had "leakage of the heart." Physical examination showed râles at the left apex and signs of cavitation in this region. The heart showed no evidence of enlargement, but there was a rumbling systolic murmur heard over the entire precordium, with its maximum intensity in the pulmonic area. The systolic blood pressure was 115 mm. Hg, the diastolic 75 mm. The remainder of the physical examination was negative except for a right dorsal, left lumbar, roto-scoliosis. The sputum examination was positive for tubercle bacilli, in large numbers. The roentgen-ray examination of the chest (figure 1) showed a cavity at the left apex 4 cm. in diameter, with several small annular shadows below it, which were interpreted as additional cavities. There was a considerable increase in density in the second left anterior intercostal space. The right lung field was clear except for a small, irregular, adventitious shadow in the second anterior intercostal space. The electrocardiogram on August 1, (figure 2a) showed marked right axis deviation, but was

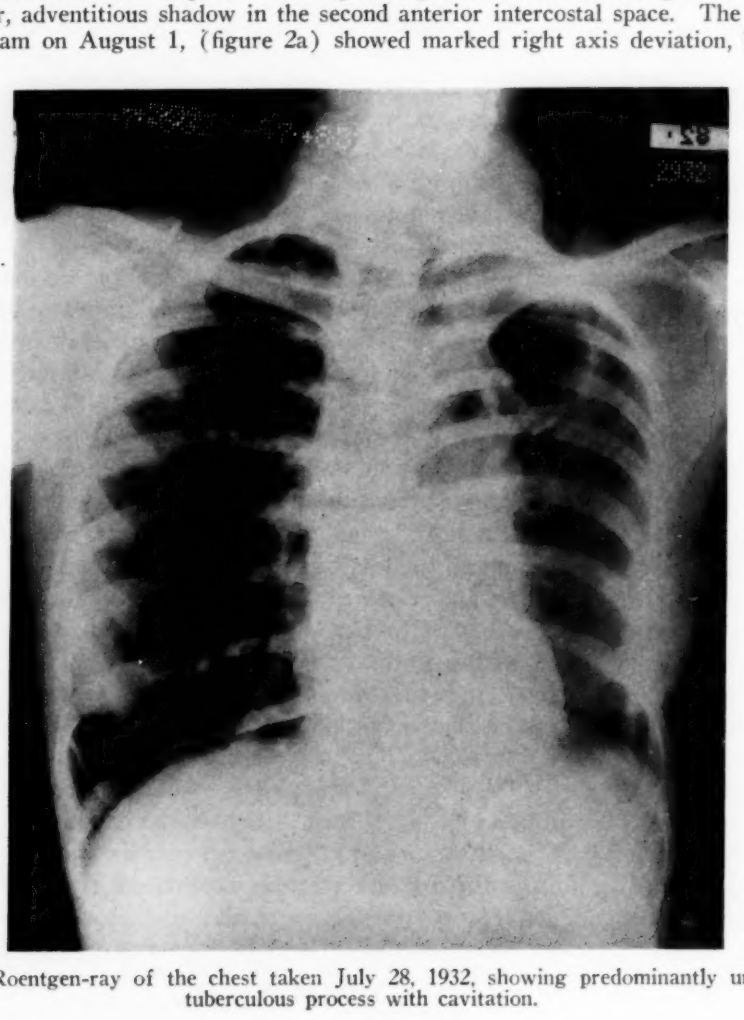

Fig. 1. Roentgen-ray of the chest taken July 28, 1932, showing predominantly unilateral tuberculous process with cavitation.

otherwise negative. The presence of marked right axis deviation in a patient with a systolic murmur of the type described was felt to justify the diagnosis of pulmonary stenosis.

Artificial pneumothorax on the left being the therapeutic procedure of choice in this case, attempts to induce it were made on three different occasions, but without success. On the fourth attempt on August 8, the needle was introduced in the lower left axillary region, with the patient on her right side. The needle had just been introduced, and no manometer oscillations had been obtained, when the patient complained of feeling faint. The needle was immediately withdrawn, but a generalized convulsion lasting about 30 seconds ensued. Following this the patient was markedly cyanotic, there was slowing of the respirations and the pulse could not be felt. Adrenalin and caffeine were administered subcutaneously. Soon after this there was recovery from the circulatory collapse and respiratory depression. When the patient became fully conscious she complained of substernal pressure. She was obviously dyspneic, and vomited frequently. An emergency chest roentgen-ray showed no pneumothorax pocket. The sensation of substernal pressure and the vomiting persisted for several hours and the patient complained of dyspnea for a period of six days following the accident. Thereafter there were no further symptoms referable to the incident and the only indication of persistent change resulting therefrom was an electrocardiographic abnormality.

An electrocardiogram was taken 2 hours and 55 minutes after the accident. This is reproduced in figure 2b. Subsequently, electrocardiographic tracings were taken at frequent intervals, and representative curves are reproduced in figure 2.

It is of interest to add that the patient's tuberculous lesion eventually became quiescent, thanks to a phrenic nerve interruption on the left, which was successful in completely closing the large cavity.

Comment

The feature of greatest interest in this case is the series of electrocardiographic changes which followed the accident described. These changes are typical of myocardial infarction. This is true not only of the progressive alterations in the form of the RS–T segment and T-deflections (figure 2b, c, and d), but also of the changes in the form of QRS. The initial upstroke of the QRS group in Lead I, present prior to the accident (figure 2a), is absent in the subsequent curves (figure 2b, c, d), in which it is replaced by a prominent Q-deflection. Changes of this kind in the QRS-deflections have been shown by Wilson and his coworkers [18] to be associated with infarction of the anterior wall of the heart. When they are associated with sharp inversion of the T-deflection in Lead I, as in the present instance, there can be very little question as to the presence of a localized lesion in the anterior ventricular wall.

As a possible cause for the myocardial disturbance suggested by the patient's symptoms and shown by the electrocardiogram we may consider three possibilities: (1) Injury to the heart by the pneumothorax needle; (2) coronary thrombosis; (3) coronary embolism.

Injury to the heart by the pneumothorax needle is mentioned because either pericarditis or hemorrhage into the pericardial sac may produce changes in the T-wave and S–T segment of the electrocardiogram suggestive of coronary occlusion. However, in this case the needle was intro-

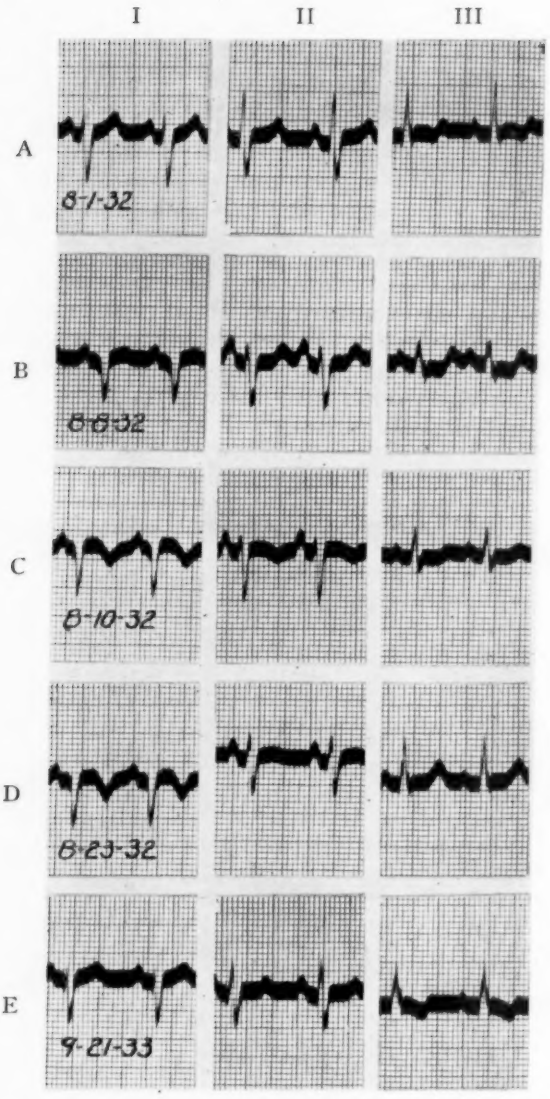

FIG. 2. Series of electrocardiographic tracings selected to demonstrate progressive changes in initial and final ventricular deflections:

(*a*) Curve taken prior to the embolic accident showing right axis deviation.

(*b*) Curve taken 2 hours and 55 minutes after the embolic accident. The initial upstroke of the QRS deflection in Lead I, noted in *a*, is now absent, and there is a large Q-wave in this lead. The S–T segment is elevated in Lead I and depressed in Lead III.

(*c*) Curve taken two days later. There is now present in Lead I, in addition to the prominent Q-deflection, a definite coronary type of T-wave inversion. The T-wave in Lead II is also inverted.

(*d*) Curve taken 15 days after embolic accident. The coronary type of T-wave in Lead I is again present in this tracing. T_2 is now upright.

(*e*) Curve taken 13 months after the accident. There is now a reappearance of the initial upstroke in Lead I and the T-waves are normal.

duced in the mid-axillary region, and to such a slight depth that this possibility is precluded. Furthermore, neither pericarditis nor hemorrhage into the pericardial sac produces changes in the initial ventricular deflections of the type seen in the present instance.

Coronary thrombosis as a cause of the myocardial infarction is practically excluded by the patient's age. There were, furthermore, no evidences whatsoever of any vascular disease, and the recovery of the patient from the cardiac standpoint has been practically complete. There is no obvious reason why coronary occlusion should complicate an attempt to produce pneumothorax and its occurrence as a pure coincidence is too remote for consideration.

Coronary embolism must, therefore, be considered as the only likely cause of myocardial infarction in this case. Whether the embolus was air or a clot cannot be stated with certainty. Vallin [19] has suggested that the mobilization of thrombi in the pulmonary vessels in the course of thoracentesis might result in embolism. Such an embolism must be considered a possibility in this instance. Saphir,[20] however, has pointed out in his review of the literature on the subject the extreme rarity of cases in which a solid type of embolus finds its way into the coronary arteries. It is far more logical, in view of the work of Rukstinat, to consider air the embolus responsible for the cardiac disturbance described.

One question naturally arises from the assumption that coronary air embolism was responsible for the electrocardiographic changes. This concerns the possibility of air remaining in the coronary arteries long enough to produce death of the heart muscle, or at least to produce changes lasting several weeks. This is a difficult question to answer. The experimental work which has been done has yielded no evidence for or against the possibility. Only by considering a somewhat analogous situation, the results of cerebral ischemia in cerebral air embolism, can a partial answer be given.

In cerebral air embolism the monoplegias and hemiplegias which result from ischemia of brain tissue are of variable duration, but it is important to emphasize that there are cases in which the paralyses persist for many days or even months. In one case observed by Villani [21] a complete left hemi-paresis persisted for four months, and a paresis and atrophy of the left arm were present until the patient's death from tuberculosis 28 months after the original embolic accident. Such persistence of paralysis can only be accounted for on the basis of profound changes in the cerebral tissues. Wever,[10] in his experimental study of cerebral air embolism, points out that, within 15 hours of air injection in dogs, liquefaction of brain cells is noted and that in three to five days there is a marked proliferation of the glial cells at the places where brain cell injury is marked. Cerebral tissue is, of course, more susceptible to injury by vascular changes than cardiac muscle, but it seems logical to assume that the changes produced by coronary air embolism are as lasting as those produced by cerebral air embolism.

Summary

A case of coronary air embolism complicating the attempted induction of artificial pneumothorax is reported. This case supports the contention of Rukstinat that involvement of the coronary arteries is an important factor in air embolism complicating artificial pneumothorax and other chest procedures.

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THE SHOCK SYNDROME IN MEDICINE AND SURGERY *

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WITHIN the past five years renewed attention has been directed to the shock syndrome. Several investigators have obtained results at variance with interpretations previously held. Yet those interpretations were advanced by men of international standing and were based upon experimental work and observations which have been adequately verified by repetition at the hands of others. The dissenting views likewise are based upon experimental evidence of apparently equally high credibility. An attempt to correlate the contradictory phases of the evidence seems appropriate. All the facts which studies on shock have established may be assembled into an intelligible picture. This problem becomes relatively simple when its parts are appropriately correlated. One fundamental concept must be comprehended: *The shock syndrome results from a disparity between the volume of blood and the volume-capacity of the vascular system.* All the pertinent facts regarding shock may be assembled about this concept as a skeletal frame. Its conditions of occurrence must be sought among factors which (*a*) decrease the volume of blood, (*b*) increase the volume-capacity of the vascular system, and in combinations of factors *a* and *b*.

Such a disparity produces circulatory failure with certain well known characteristics. Rapid weak pulse, low blood pressure, rapid shallow respirations, decreased temperature and pale clammy skin are prominent features. Vomiting and diarrhea are frequent, and these discharges often are blood-tinged. This condition is accompanied by a diminution in blood volume and by marked hemo-concentration. The hemoglobin and red cells are usually increased by 20 to 50 per cent. This feature provides a valuable clinical test for recognizing shock and for differentiating it from hemorrhage or other conditions. Attention is invited to a brief consideration of the mechanism by which shock develops, and of the factors concerned.

Decreased Volume of Blood. Loss of blood by hemorrhage produces a disparity by decreasing directly the volume of blood. This results in the characteristic features of shock with these exceptions: following hemorrhage the concentration of blood is lowered; and the decreased volume may be restored by the injection of fluids. In shock from other causes the concentration of the blood is increased, and injections of fluid are usually ineffective.

A decreased volume of blood may develop indirectly by the transudation of plasma through the walls of capillaries whose permeability has been increased by various agents to be discussed later. Increased capillary permea-

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bility is present in shock from various causes, and produces the hemo-concentration which is so characteristic of this condition.

Increased Volume-Capacity of the Vascular System. Normal tissues have a supply of capillaries adequate to their maximal circulatory needs. Normally only a small fraction of these are open to circulation simultaneously. If all the capillaries in the skeletal muscles alone were open simultaneously, their volume-capacity would be sufficient to contain the entire blood of the body (Krogh). Other areas, as the respiratory system or the gastro-intestinal mucosa, have an equally large supply of minute vessels. Under conditions to be discussed, these minute vessels become atonic, relaxed and unresponsive to nerve impulses or other agents which normally produce contraction (Krogh, Hooker). They withdraw blood from circulation like a sponge absorbs water. The volume-capacity of the vascular system is greatly increased. The circulation fails not because of cardiac weakness, but because of insufficient return of blood from the tissues. The heart is not a suction pump; it cannot draw blood out of the tissues, it can only pump the fluid supplied to it.

Many conditions may produce capillary atony and dilatation. The experiments of Dale and his associates showed that intravenous injections of histamine produce this type of circulatory failure. The capillaries and venules were dilated and filled with blood, their permeability was increased, edema of the tissues and hemo-concentration occurred, the blood volume was decreased by 40 per cent, blood pressure fell to low levels, and the animals died with the characteristic evidences of shock.

Traumatic Shock. A wealth of observations on traumatic shock was published during and immediately following the World War.* It was shown that shock is accompanied by an increased concentration of blood and by a marked diminution in the total volume of blood in circulation; that the fall in blood pressure is not due to cardiac weakness or to vasomotor deficiency. The hearts of patients and of experimental animals in shock were able to maintain normal blood pressure if supplied with fluid and with vascular resistance; the arteries were not atonic but were contracted to the maximum.

The reports of these investigations indicate that traumatic shock results from the absorption of injurious substances from traumatized tissue; that these substances produce capillary dilatation and increased permeability resulting in stagnation of blood in systemic areas; that this sequestration of blood and the transudation of plasma into the tissue reduce the effective blood volume. Increased concentration of blood and the circulatory failure characteristic of shock result. Subsequent investigations have shown no discrepancies in this explanation but have corroborated its essential features.

It is remarkable that the gross and microscopic changes characteristic of shock escaped the attention of early observers. A number of workers noted

* Of especial value are the Special Reports 25 and 26 of the Medical Research Committee, London, 1919, H. M. Stat. Off.

such features as congestion, edema and capillary hemorrhages in the tissues in experimental shock. But no one emphasized that these visible changes are characteristic of shock, and are etiologically related to its development. Neither was it emphasized that observations on the concentration of the blood are useful in recognizing the shock syndrome clinically.

I have examined many records of postmortem examinations on soldiers following severe shell-fragment injuries. Marked congestion and edema of the viscera, and capillary hemorrhages in mucous and serous surfaces had been noted by the dissectors regularly in those who died of shock. Frequently such descriptive phrases as "wet autopsy" were used to denote the contrast with the "dry autopsy" seen following death by hemorrhage. But apparently no relation was seen between these findings and the shock mechanism.

Moon and Kennedy made gross and microscopic studies of the organs in experimental shock produced without local injury or hemorrhage. The characteristic manifestations of shock, including hemo-concentration, followed the implantation of small amounts of fresh, finely chopped dog muscle into the peritoneal cavities of normal dogs. Likewise, shock followed injections of sterile watery extracts of normal muscle, extracts of traumatized muscle; and was observed following trauma to the muscles of normal dogs. In each of these instances the postmortem findings were identical in character. Since these findings are of marked significance they will be described briefly for purposes of subsequent reference.

Experimental Shock: Tissue Changes Characteristic of Shock. The veins in subcutaneous and peripheral areas are collapsed and relatively bloodless. The viscera are deeply congested and have a purplish diffuse cyanotic color. This is especially prominent in the lungs, liver and gastrointestinal tract. The venules of the visceral peritoneum are engorged and distended. Those along the mesenteric attachment are especially prominent. Usually the spleen is contracted and bloodless, though occasionally it also is engorged. There are varying quantities of thin, blood-tinged fluid in the peritoneal, pleural and sometimes in the pericardial cavities. The mucosae of the respiratory and gastrointestinal tracts are swollen and have the appearance of red velvet. There are numerous petechial hemorrhages in the lungs, in the pleural and pericardial surfaces, in the intestinal mucosa, occasionally in the lining of the gall and urinary bladders, and in the meninges. Edema of the lungs and mucosae and serous effusions are most marked when shock develops gradually and death is not immediate. When shock ending in death develops rapidly, congestion and capillary hemorrhages are marked and edema is a less prominent feature. The fluid present in the stomach usually contains "coffee-grounds" flocculi which give a positive test for hemoglobin. The fluid in the stomach and bowel contains quantities of serum albumin. The undiluted fluid often forms a solid coagulum when heated.

On microscopic examination there are marked dilatation and engorge-

ment of the capillaries and venules in each of the organs mentioned. There are numerous minute areas of hemorrhage, apparently from dissolution of capillary walls, and tissue edema is present in varying degrees. The adrenals participate in these circulatory changes in a degree similar to that seen in other organs, but they show no other changes.

These observations indicate a widespread loss of tonus affecting the capillaries and venules. The circulatory disparity in this instance results from an increased volume-capacity of the vascular system or, what is equivalent, from inability of the vascular system to contract with its normal tonus upon the contained blood.

There was evidence that the minute vessels were abnormally permeable to blood plasma. This gave rise to edema, serous effusions, and to the transudation of fluid from the blood into the gastrointestinal canal. Such loss of fluid lowers the blood volume and produces hemo-concentration.

Experimental Shock from Poisonous Substances. Many chemicals and drugs produce injurious effects by causing atony and dilatation of the peripheral vessels, especially the capillaries and venules. Such substances are known as capillary poisons (Krogh, Heubner). Capillaries are exceedingly delicate structures and easily injured. Any condition or agent which injures them increases the permeability of their walls (Landis). This allows blood plasma to escape into the tissue spaces, producing edema and resulting in hemo-concentration. Heubner (1907) found that the intravenous injection of gold chloride was followed by a progressive decline of blood pressure ending in death in a few minutes. He gave the first detailed description and correct interpretation of the visible changes characteristic of shock, which I have found. The finest venules, especially in the abdominal viscera, were heavily congested. The peritoneal surfaces of the bowels were rose red or bluish red. The mucosae were dark red and contained numerous hemorrhagic flecks. Similar minute hemorrhages were present in the surfaces of the liver, spleen and kidneys. Blood-tinged fluid was present in the serous cavities. The lungs were deep red and contained numerous ecchymoses in their substance and also in the pleura. Blood flowed freely from the cut surfaces of the organs. The outstanding microscopic feature was distention and engorgement of the minute vessels in all the tissues. There were numerous capillary hemorrhages in the substance of the organs, especially the lungs, liver and kidneys. These are exactly the changes found in experimental shock. He concluded that the circulatory failure resulted from the widespread dilatation of the capillaries and venules. The animals had bled to death into their own capillaries.

Other poisons produce similar effects. MacNider found that the intravenous injection of mercuric chloride in dogs produced shock followed by death. Landis found that mercuric chloride 1 : 10,000 dilution, caused capillaries to become seven times more permeable than normal capillaries. Alcohol, urethane, veronal and other anesthetic drugs produce similar effects. Blalock, Robinson, Parsons and others noted that the barbital anesthesia

which was used in experimental traumatic shock occasionally resulted in "spontaneous shock" when no experimentation had been done. I have seen a normal dog manifest the classical picture of shock following the intravenous injection of sodium pheno-barbital, 0.3 gm. per kg. of body weight. The blood pressure fell 94 mm. in the course of three hours. Death followed a second smaller injection, and the postmortem findings were identical with those following shock from other causes.

Injections of peptone, albumose, or other products of protein cleavage will produce capillary dilatation and permeability resulting in the shock syndrome (Abel et al.; Whipple et al.; Krogh: p. 241). The same is true of injections of extracts of normal tissues (Delbet; Bayliss; Moon and Kennedy). Bacterial suspensions and toxins produce similar effects. Bacteria-free broth in which *B. Welchii* has grown, will produce shock if injected intravenously. I have produced the same effect by intravenous injection of killed broth cultures of enterococcus. This produced profound prostration, blood-tinged vomitus and diarrhea, rapid respiration and pulse, falling temperature, hemo-concentration and death within 48 hours. At postmortem the same changes were found as in shock from other causes.

The relationship between metabolic poisons and the shock syndrome rests largely upon clinico-pathologic evidence. The experimental use of metabolic poisons is impracticable, since they have not been isolated. It is known that bile is toxic, and that jaundiced patients frequently manifest toxemia. The rupture of a gall-bladder into the peritoneal cavity is followed by shock. The intravenous or intraperitoneal injection of sterile bile produces death with shock-like manifestations (Horrall and Carlson). At postmortem the characteristic evidences of shock are seen in the viscera. Apparently bile in sufficient concentration in the circulating blood is injurious to the capillaries, and produces effects like those of other capillary poisons.

Anoxemia. Deficiency of oxygen is an important factor influencing capillary tonus (Cannon, Krogh, Heimberger, Landis). Anoxemia of relatively low grade, such as may be produced by temporarily occluding a vessel, causes dilatation and increased permeability of the capillary walls, with resulting edema and hemo-concentration.

Disturbances of Vasomotor Control. It is well known that vascular tonus is influenced by nerve stimuli. Freeman found that prolonged arterial constriction, produced by the continuous injection of adrenalin or by hyperactivity of the sympathico-adrenal system, decreased the volume of blood in circulation. This was interpreted by him and by Cannon as due to partial asphyxia of the tissues resulting from maximal arterial constriction. However, the corpuscular elements were also decreased and there is no record that the subsequent condition was that of shock or that the pathological tissue changes characteristic of shock resulted. Erlanger and Gasser also found that injections of adrenalin caused a decreased volume of blood, but although they used larger doses than did Freeman, they were unable to produce other manifestations of shock by this mechanism. A

decreased volume of blood does not of itself constitute shock. Is it possible that the arterial constriction merely caused a considerable volume of blood to be stored in the normal reservoirs, the spleen and liver?

Freeman attempted to produce shock by generalized vaso-dilatation. Prolonged stimulation of the depressor nerve reduced the blood pressure from 145 to between 60 and 80 mm. of mercury. These low pressures were maintained for 95 minutes but returned promptly to normal upon cessation of stimulation. The low pressures resulting from such vaso-dilatation were accompanied by a slight loss of blood volume but not by hemo-concentration. These experiments did not produce shock.

Eppinger found that low blood pressure, decreased blood volume and other evidences of shock followed the injection of cocaine about the vaso-motor center in the medulla. The manifestations were not accompanied by a transudation of plasma through the capillary walls nor by hemo-concentration. The circulation gradually returned to normal and the animals recovered without developing shock.

Dale and Laidlaw found that acetyl choline produces marked arterial dilatation without affecting the veins and capillaries. Thus its effect on the circulation resembles that of arterial relaxation from vasomotor insufficiency. By slow infusion of acetyl choline the blood pressure was maintained at low levels for varying periods of time. This did not result in capillary permeability or hemo-concentration. The heart's action remained efficient and a return to normal occurred when the infusion was discontinued. Shock did not develop in these experiments.

It seems that one factor of the grave progressive shock syndrome is lacking in these experiments: The tonus of the capillaries apparently is not affected, nor their permeability increased. Hence edema and hemo-concentration do not develop. It is conceivable that prolonged sympathico-adrenal stimulation or vasomotor inhibition might result in anoxemia or asphyxia of the capillaries. This in turn would be followed by capillary dilatation and permeability, and would complete the picture. Any lesion of the central nervous system or defect of nerve-vascular control which would cause capillary atony would produce a circulatory disparity resulting in the shock syndrome.

Deficiency of Adrenal Cortex. Recent experimental work (Swingle et al.; Britton; Stewart and Rogoff; Banting and Gairns; Hartman et al.) on the adrenals indicates that one function of the adrenal cortex is to maintain venous and capillary tonus. Animals deprived of the cortical hormone develop the characteristic manifestations of shock. There are decreased blood volume, increased concentration of blood, low blood pressure, and an insufficient return of venous blood from the periphery. There is transudation of plasma through the capillary walls. Bloody vomitus and diarrhea are frequent. Extreme weakness, prostration and coma precede death. Many of the visible circulatory changes characteristic of shock are noted in the postmortem records, although none of the authors comment on

their significance. Apparently the lack of adrenal cortical hormone causes vascular atony with increased capillary permeability, and leads to death by a mechanism similar to that in shock from other causes. The circulation returns to normal, and may be maintained indefinitely, by injections of adrenal cortical extract.

The development of shock from lack of adrenal cortical hormone furnishes a significant illustration of the main thesis of this discussion. Increased volume-capacity of the vascular system, arising in this instance from a physiological deficiency, produces the typical shock syndrome. It is not probable that adrenal cortical insufficiency is an important factor in clinical cases manifesting the shock syndrome. I have not found visible evidences of adrenal abnormality in any human case or in experimental shock in animals. It would be of value to find whether adrenal cortical extract would restore the tonus of the minute vessels in shock arising from other causes.

Recently several writers (Parsons, Phemister, Blalock, et al.) have interpreted the shock syndrome as due entirely to loss of blood and fluid at the site of the trauma or injury. This mechanism obviously will not apply to all instances, such as those of shock following the injection of histamine, tissue extracts and various capillary poisons, the implantation of muscle substance in the peritoneal cavity, nor to shock developing from adrenal cortical insufficiency. In such cases there has been no local loss of blood or plasma. The authors have also overlooked the fact that, even where considerable local loss of fluid has occurred, the postmortem examination shows systemic vascular atony especially of capillaries and venules. Obviously any loss of fluid locally, as in extensive burns or physical trauma, will contribute to the circulatory disparity, and its importance will be proportionate to the amount of blood and fluid lost.

It appears from the foregoing considerations that the shock syndrome results most frequently from dilatation of capillaries and venules plus leakage of plasma through capillary walls whose permeability has been increased. This feature has been present in shock produced by various means. It is a constant postmortem feature following shock from diverse causes. In the experiments which produced low blood pressure by simple vascular dilatation without capillary injury, shock did not result. A simple loss of blood or of plasma, the vascular walls remaining normal, does not progress but tends to restoration by physiologic processes. Fluid is absorbed from the tissues, or that supplied therapeutically is retained in the circulation. In shock the reverse is true. Fluid is neither absorbed nor retained and further loss by vomiting, diarrhea, effusion and by edema is progressive.

One concludes that increased capillary permeability is an essential factor in the mechanism by which shock progresses.

The Clinical Occurrence of Shock

The rapid development of shock in a healthy person following extensive injury or surgery is a condition readily recognized. The gradual development of the same type of circulatory failure during some severe illness may not be recognized or may be attributed incorrectly to heart failure. Atchley discussed such cases as "medical shock" and cited instances in severe influenza, pneumonia and diabetic acidosis. He described the development of shock following an overdose of pneumococcal vaccine, and following a snake bite in which the venom apparently entered a vein. He attributed the circulatory failure to loss of capillary tonus, causing the vascular bed to become larger than the blood volume. He recommended the intravenous injection of hypertonic dextrose solution, of saline solution, and transfusion of blood as effective therapeutic measures.

Warfield recognized the development of shock in typhoid and other severe infections. He emphasized hemo-concentration as a feature and advised intravenous injection of fluids, or transfusions. He found such agents as strychnine, caffeine, adrenalin and pitressin of value but believed that digitalis was contraindicated, since cardiac weakness is not a factor.

Eppinger gave a comprehensive discussion of shock occurring under various conditions. He drew sharp distinctions between shock and heart failure. He emphasized hemo-concentration as an essential feature and explained it as due to leakage of plasma through atonic and permeable capillary walls. He reported cases of shock resulting from severe infections such as typhoid, cholera, scarlatina, pneumonia, peritonitis, and others; following poisoning with mercuric chloride, veronal, and other drugs, following meat poisoning, metabolic intoxications such as icterus, and following severe burns and other conditions. He indicated as appropriate therapeutic measures those which would stimulate the vasomotor center, those which would cause contraction of the peripheral vessels and of the blood reservoirs, those such as injections of fluid or transfusion of blood which would cause an actual increase in the blood volume, and those which by mechanical support, as abdominal binders, might facilitate a return of venous blood from the system.

Moon reported the occurrence of shock following burns, toxemias of various origin, poisoning with various substances, in severe acute infections, and in abdominal emergencies such as intestinal obstruction, hemorrhagic pancreatitis, mesenteric thrombosis, perforation or rupture of a viscus, etc. In each of these conditions the clinical signs of shock were present and in each there was marked hemo-concentration. At postmortem the findings corresponded exactly to the description already given. He emphasized that observations on hemo-concentration are of value in recognizing shock clinically and in estimating its severity.

A few details of the features present in some of these instances may be of interest. The typical clinical picture of shock develops following a severe superficial burn. The pulse is rapid and weak, the respirations rapid

and shallow, and the blood pressure declines progressively. Marked hemoconcentration takes place, as shown by red cell count, hemoglobin content and specific gravity of the blood. Thirst may be marked but water taken by mouth is not readily absorbed and is followed by vomiting of fluid containing blood. The temperature at first may be sharply elevated, but later becomes subnormal. The skin in areas remote from the burn becomes cold and clammy. Marked pulmonary congestion and edema develop. The urine becomes concentrated and often contains hemoglobin and albumin. Bloody diarrhea may be present. The mental state becomes clouded. Restlessness, delirium or coma may precede death.

The postmortem findings (Bardeen, Pack) are exactly those found in shock from other causes. They are identical to those described by Heubner and Dale following the injection of metallic salts or of histamine into animals.

Lewis and his associates have shown that histamine is a constituent of the normal skin, and that it is released in response to any type of injury to the cells. The local effect of this is to produce dilatation and increased permeability of the capillaries, resulting in congestion and edema. If a minute burn causes sufficient histamine to be released to affect the capillaries locally, the large amount released from extensive burns would produce similar capillary phenomena, systemic rather than local in distribution.

The degree of hemo-concentration following burns is proportional to the severity of the burn and to the degree of shock. Tappeiner (1881) reported four fatal cases of burns in which the erythrocytes ranged between 7,800,000 and 8,960,000. In five of Locke's 10 cases the erythrocytes reached 9,000,000. Underhill and his associates made blood studies in 20 cases of burns of varying degrees. In these the hemoglobin percentage ranged between 114 in the milder cases and 226 in the most severe.

I have reported elsewhere three cases illustrative of varying degrees of shock following burns. Three men were superficially burned following a collision in which a gasoline tank burst and ignited. The burns were of the second and third degree involving chiefly the legs, arms and faces. Shock was a marked clinical feature in each case. The burns varied somewhat as to the amount of skin involved; and likewise the degree of shock varied. The man having the most extensive burn had a red cell count of 8,350,000 and the hemoglobin was correspondingly high. He became semicomatose and died of circulatory failure within 48 hours. The postmortem picture was that regularly found following burns or following shock from other causes.

Another man, burned at the same time but whose burns were slightly less extensive, died of secondary pneumonia 11 days later. His condition of moderate shock, as shown by blood pressure, blood concentration and general condition, continued during the 11 days. At postmortem the viscera showed the circulatory changes characteristic of shock or of burns. In addition to these, pneumonia of irregular type and distribution was

present. This feature is especially significant. Lungs whose circulation is impaired and whose spaces are filled with edematous fluid, present a stage already set for the final act—the development of pneumonia. This is probably the mechanism by which terminal pneumonia develops after severe burns.

The third man who was burned recovered. The blood concentration, shown in the following chart, declined gradually as the patient's condition progressed toward recovery.

TABLE I

Date	Specific Gravity	Hgb.	Red Cells
Dec. 14	1.075	120+	6,700,000
" 15	1.070	112	5,400,000
" 16	1.063	110	5,000,000
" 17	1.070	116	5,200,000
" 18	1.068	115	5,100,000
" 19	1.066	110	4,990,000
" 20	1.062	106	4,900,000
" 21	1.055	99	4,630,000
" 22	1.048	74	3,530,000
" 24	1.045	87	3,820,000

The circulatory phenomena following burns are identical with those of histamine shock. The mechanism of origin apparently is not different from that of shock from other causes.

Drugs and Chemicals. The characteristic features of shock occur in poisoning with various drugs. A man, aged 34, took an unknown amount of sedormide. Profound narcosis resulted and he was unconscious for 18 hours. On admission to the hospital the red cells were 6,030,000 and the hemoglobin 118 per cent. On the following day the temperature was 97°, the pulse 130 and the blood pressure 110 mm. Hg systolic, and 70 diastolic. Adrenalin, atropine, caffeine and pituitrin were given as stimulants. Fluids were given by mouth, by hypodermoclysis and by glucose solution intravenously. These were ineffective. Death occurred within 72 hours. The postmortem findings were characteristic of shock as previously described. Bronchopneumonia in an early stage was also present.

Mercuric chloride poisoning frequently produces the shock syndrome. Such a case was reported by Moon and Crawford. A man, aged 39, swallowed 175 gr. of mercuric chloride. The development of profound shock resulted fatally in 37 hours. Postmortem examination showed marked congestion and edema of the viscera, particularly of the pulmonary and gastrointestinal tracts. The lungs were markedly congested and engorged. Their combined weight was 1500 gm. above normal, due to congestion and edema. About 1500 c.c. of blood-tinged fluid were present in the serous cavities. These two locations alone accounted for the loss of 3000 c.c. of fluid withdrawn from the circulation. Other organs were congested and edematous; capillary hemorrhages were numerous everywhere. This case illustrated strikingly the effects of severe, widespread injury to the capillaries.

The intravenous injection of arsenical compounds for therapeutic pur-

poses sometimes is followed by collapse ending in death. The postmortem findings in such cases are the same as in early death in mercuric chloride poisoning. Arsenical poisons are included among capillary poisons by Heubner, Krogh and others.

Toxemias of Metabolic Origin. Severe toxemias may result in circulatory collapse similar to traumatic shock. The following case is an instance:

A white man, aged 41, had a history of progressively deepening icterus, nausea, vomiting, clay-colored stools, weakness and malaise. The clinical diagnosis was acute yellow atrophy of the liver. On the day following admission the blood pressure was 106 mm. Hg systolic and 60 diastolic; two days later it was 100 systolic and 56 diastolic. The decline in blood pressure was accompanied by a rise in erythrocytes from 4,490,000 to 6,240,000 and of hemoglobin from 81 to 110. Pulmonary edema developed which did not respond to atropine, but increased progressively. The pulse became rapid and weak. Glucose solution given intravenously at intervals caused slight temporary increase in blood pressure. Coma, a declining temperature and failing circulation preceded death. The postmortem examination showed acute hepatic necrosis and the circulatory changes characteristic of shock.

Toxemia associated with pregnancy may produce the shock syndrome. The following case is an instance. A white woman, five months' pregnant, became ill and was brought to the hospital. She had repeated severe convulsions, was very restless in the interims, had constant thirst and dyspnea. The blood pressure was 220 mm. Hg systolic and 180 diastolic when the patient was first examined. The pulse became rapid, weak and irregular. The lungs became congested and gave signs of edema. The blood pressure declined rapidly, and extreme prostration developed. The administration of caffeine, atropine, strychnine and the inhalation of oxygen were ineffective. Deep cyanosis and coma preceded death. At postmortem the circulatory findings were the same as in each of the conditions previously described.

In cases of eclampsia, of acute obstructive jaundice and of diabetic acidosis, terminating with clinical evidences of circulatory failure, I have found the same visible evidences of capillary atony.

Abdominal Emergencies. Several grave pathologic conditions arising within the abdomen produce the shock syndrome characteristically. One of these is acute pancreatitis. A young woman suffering from acute hemorrhagic pancreatitis entered the hospital. She had a rapid weak pulse, rapid respirations, cold pale skin and falling blood pressure. No operation was done; the treatment was entirely symptomatic; she died of circulatory failure within 48 hours. Only one blood count was made. The red cells were 6,400,000 and the hemoglobin 112. At postmortem the visible evidences of shock were present in characteristic form. De Takats and Mackenzie reported nine cases of hemorrhagic pancreatitis, in all of which the red cells

were above five million and the hemoglobin correspondingly high. One case had 8,300,000 red cells and 140 per cent hemoglobin. They recognized the shock syndrome in each case and stated that blood counts furnished a means for determining the degree of shock.

Several authors have interpreted the syndrome which follows acute intestinal obstruction as shock. Yet the cause for death in this condition is still a much debated question among surgeons (Cooper, for review). That the essential clinical features of shock develop following volvulus or strangulation will not be questioned. I have recently reviewed the postmortem data on 26 cases in which intestinal obstruction was a feature. The majority of these examinations were made in the period before the gross and microscopic changes characteristic of shock were recognized. But in all cases such features as congestion and edema of the lungs and other viscera, effusion into serous cavities and petechial hemorrhages were noted.

We made experimental high intestinal obstructions in four dogs to secure further evidence on this point. In each instance the characteristic shock syndrome accompanied by hemo-concentration developed. And in each instance the gross and microscopic evidences were of the same character as previously described.

A similar development may follow severe trauma to the abdomen without penetration of the abdominal wall. Mesenteric thrombosis, and perforation or rupture of the abdominal viscera may produce shock. In each of these instances postmortem examination has shown the same visible circulatory changes as described before. It appears that substances producing capillary atony are derived from the bowel tract more readily than from some other areas. Surgeons have observed that shock frequently develops following abdominal operations which have required much handling of the intestines.

Infections. Many authors have noted the shock syndrome in acute infections. It is well known that cholera and gas bacillus infection develop into shock. Such observations coupled with experimental evidence indicate that bacterial products and substances derived from infected tissue may abolish capillary tonus as do other capillary poisons. My curiosity concerning the shock syndrome was first aroused during the pandemic of influenza in 1918–1919. Observations were made then which were not interpreted satisfactorily until recently. Many of the most severe cases died within two or three days of the onset. A few died within 24 hours. These rapidly fatal cases died of circulatory failure which the clinicians termed collapse or shock. Red cell counts in such cases ranged from 6,000,000 to 8,000,000 and the hemoglobin was correspondingly high. The clinicians soon recognized this as a grave prognostic sign. In such cases congestion and edema of the lungs developed rapidly and death resulted. Postmortem examinations showed wet bloody lungs and extreme capillary congestion of the mucosae of the pulmonary and gastrointestinal tracts. Frequently there was an effusion of reddish fluid in the serous cavities. No pneumonia

was present in these fulminating cases. The gross and microscopic features were indistinguishable from those following severe burns or following shock from other causes, as was learned later.

Underhill and Ringer made blood studies in 43 cases of influenza. In severe cases there was marked concentration of the blood, with hemoglobin values ranging from 110 to 140. Death resulted in each such instance. No hemo-concentration was found in the milder cases, and there was no instance of it among any patients who recovered. They concluded that the degree of hemo-concentration was an index of the severity of the illness and that it was of value in prognosis. Their description of the postmortem findings in fulminating cases agrees with those regularly found in such cases. These descriptions will apply with equal accuracy to the organs following death from burns. Neither Underhill and Ringer, nor any other author I have found, suggested a relationship between the circulatory changes described and the mechanism of circulatory failure which caused the death.

Pneumonia Following Shock

In influenza of somewhat less severity the patients lived from seven to 15 days. Congestion and edema were marked but were not so extreme as in those who died early. The lungs were wet and bloody, and pneumonia of very irregular type and distribution was present. Bacteriologic studies gave no consistent results. Various organisms which are common invaders of the respiratory tract were found. Mixed infections were the rule. The gross and microscopic features were indistinguishable from those of secondary pneumonia following burns.

I have compared the gross and microscopic features of pneumonia following influenza, burns, surgical operation, intoxications of various kinds, and severe acute infections. I find no essential differences in their morphologic features nor in the bacteria which are associated. I believe that the same mechanism is operative in each of these groups of cases. It must be emphasized that the shock syndrome occurs in varying degrees and with varying rapidity. Shock of moderate degree and gradual development is of frequent occurrence. It is accompanied by pulmonary congestion and edema, and leads to death by secondary pneumonia. In material from 100 autopsies on adults, secondary pneumonia of this type occurred in 16 cases. Eight cases occurred following surgical procedures and one case each occurred in the following conditions: ulcerative colitis, acute hemorrhagic pancreatitis, drug poisoning (sedormide), obstructive jaundice, eclampsia, superficial burn of skin, diabetes with acidosis, and peritonitis. These presented the same type of pneumonia and were preceded by pulmonary congestion and edema in each case.

Summary

The shock syndrome results whenever the volume of blood inadequately fills the vascular system. This may result from loss of blood or fluid, or from atony or dilatation of the vascular walls especially the capillaries and venules. Combinations of these two factors are the rule.

Circulatory failure of this type results not from cardiac or vasomotor inefficiency, but from an inadequate return of venous blood from systemic areas.

Increased concentration of the blood is a constant feature of shock. This is of clinical value both in recognizing the condition and in determining its degree.

Shock produces characteristic changes demonstrable by postmortem examination. These consist of marked capillary and venous congestion of the viscera, edema of lungs and mucosae, petechial hemorrhages in serous and mucous surfaces, and effusion of fluid into serous cavities.

Shock occurs not only following extensive surgery or trauma. It is seen in a wide variety of clinical conditions including extensive burns, poisoning with various substances, metabolic intoxications, abdominal emergencies and severe acute infections.

Cerebral hemorrhage and other lesions of the central nervous system may terminate in shock, the mechanism of which is not evident. Perhaps prolonged vasomotor disturbance results in tissue asphyxia which in turn causes capillary atony and permeability.

Shock develops in varying degrees. Maximal degrees lead to death by circulatory failure. Lesser degrees may be followed by recovery or by death from pneumonia.

Many cases of secondary pneumonia have their origin in this type of circulatory disturbance.

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ATOPIC ANNOYANCES IN THE COURSE OF PULMONARY TUBERCULOSIS *

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THE word "atopic" is used in this paper to characterize spontaneous acquired sensitization to a foreign protein. This is an extension of Coca's [1] definition; but "allergy" means one thing to the allergist, another to the immunologist. For the purpose of the present discussion it is desirable to employ a term that excludes the delayed inflammatory reaction of the infected individual to tuberculoprotein, a reaction which students of tuberculosis generally describe as "allergic."

Atopic manifestations, especially hay fever, are often seen in cases of pulmonary tuberculosis. In 1925 I recorded the study,[2] from the viewpoint of the allergist, of a series of tuberculosis patients with asthma, and the following year reported the relief of hay fever by intradermal injections of pollen extract during the attack, commenting on the suitability of this method for tuberculosis patients because of the low dosage employed. Three years ago, the better to determine the frequency and importance of atopic complications in tuberculosis, I began to make, as part of the examination of all patients in a small sanatorium near Phoenix, a careful investigation as to the presence of sensitivity. This investigation included a detailed personal and family history, daily observation, and serial blood counts with particular attention to eosinophilia. When suspicious symptoms occurred the patient was skin tested; when indicated, desensitization was undertaken, the diet was modified, and the effect of adrenalin was tried. More recently residence in an allergen-free room has been used to aid diagnosis in doubtful cases. Because of the prolonged observation and control of the patients incident to their hospitalization for tuberculosis, it has been possible to establish in most cases whether or not the presenting symptoms were atopic in their origin.

The clinical material studied was that usual to sanatoriums in the Southwest: adults of both sexes, most of them with chronic tuberculosis, 70 per cent of them far advanced. They had the accepted institutional care, with considerable emphasis on rest; comfortable quarters, ample food, and a rather high incidence of intervention, especially artificial pneumothorax. In the mild climate of this region they lived out-of-doors 12 months of the year. Their average sanatorium residence was 8-1/3 months, but because some were old patients when this study was undertaken, and because of the follow-up system employed, their period of observation varies from four months to four years, and averages nearly two years.

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Two hundred and fifty consecutive tuberculosis patients are included in this study. Fifty patients, one-fifth of the total number, showed during the period of observation clinically evident sensitization to identified foreign proteins. Four others had symptoms quite as typical, but their atopens could be demonstrated only by the therapeutic test.

Sensitivity to Pollens. In 34 cases sensitization to pollens was indicated by skin tests, confirmed by the effect of pollen therapy, and in certain instances further substantiated by the relief afforded by residence in the filtered air of an allergen-free room.

Sixteen of these patients had ordinary hay fever, with or without pollen asthma. Their ailment was easily controlled by intradermal pollen therapy and it did not perceptibly affect the symptoms or the course of their tuberculosis. But the remaining 18 of the pollen-sensitive presented a quite different picture, one that would hardly have been recognized for what it was without special study. Their nasal and conjunctival symptoms were slight; distinct asthmatic seizures did not occur. Instead, their pollenosis expressed itself by increased cough, increased expectoration with thin frothy sputum, and malaise. Some patients, during these apparent exacerbations, had elevation of temperature a degree or more above their usual normal. Examination of the chest showed a marked increase in moisture, not only over the bases but over the areas of heavier involvement. Piping râles and wheezing breath sounds were heard in most cases.

Chest roentgenograms, however, failed to reveal any unfavorable change, and the blood picture remained about as usual, except that the eosinophiles were increased. That such episodes were caused, not by colds or by localized extensions of tuberculosis, but rather by atypical manifestations of pollen sensitivity, was further shown by the fact that they were coincident with exposure to the offending pollens; the local reactions to the intradermal injection of the implicated pollens were unmistakably positive, and such therapy was followed by prompt relief. These atypical pollen patients showed a lesser degree of skin sensitization than was present in those with typical hay fever, and they required a somewhat larger dosage, over a longer period of time. It is of interest that this same type of clinical reaction to pollen occurred repeatedly in those individuals who were subject to it, either in a later season or when for some reason pollen therapy was stopped too soon.

The mechanism of these atypical pollen responses seems to be that of a mild continuous asthma acting on bronchi damaged by tuberculosis. In most cases the systemic effect, if any, was limited to a temporary loss of weight and impairment of the general health. In three instances, however, the pollenosis had gone untreated for some time, and it may have been related to the relapses which followed. It is reasonable to suppose that disturbed rest, increased lung symptoms, and worry over these untoward developments would in time impair the body's resistance to the progress of tuberculous disease. The case history now presented illustrates some of

the points mentioned, as well as the advantage of knowing, before they become clinically manifest, the sensitizations of a tuberculosis patient.

Case 1. J. C., male, aged 31. His mother suffers from hay fever and migraine; he himself was subject to ragweed hay fever and "sinus trouble" in Chicago for several years. In 1931, as shown by films of that date, he had tuberculosis involving chiefly the right upper lobe. After a year in a sanatorium he was discharged as arrested, and went to work. He remained well until the fall of 1933, when he had an attack of what he thought was sinus trouble; he coughed considerably, wheezed a little, and lost weight. He must have had active tuberculosis at that time, for when he came to Arizona and entered St. Luke's Home in November 1933 he had well marked active disease in the right lung, with positive sputum, and the usual constitutional symptoms. His skin tests at that time showed reactions not only to Eastern ragweed, but to all the local members of the ragweed group.

An expansile pneumothorax was induced, and the patient became free from symptoms, except for a scanty sputum which was negative and remained so. In March, with the pollination of *Franseria deltoides*, he began to cough, and his sputum increased to nearly 2 ounces (50 c.c.). His eosinophile cells rose from 80 to 820 per cu. mm. Under treatment with the pollen of *Franseria deltoides* all his symptoms subsided. In June he was moved to the mountains for the summer, and there in August he encountered the pollens of *Ambrosia psilostachya* and *Franseria acanthicarpa*. His symptoms returned as before, and again subsided promptly under appropriate therapy. In October he returned to Phoenix and there was exposed to the pollen of false ragweed, *Franseria tenuifolia*. The same experience was repeated; at this time his eosinophiles rose from zero to 402 and dropped again as tolerance was established by intradermal therapy with the specific pollen. None of these episodes interfered with his treatment for tuberculosis. His course, as measured by clinical and laboratory standards, was continuously favorable.

Sensitivity to Foods. Sixteen patients were found to be sensitive to foods alone, and seven of the pollen-sensitive group reacted to foods as well. The commonest manifestations of food sensitivity were those so familiar to the sanatorium worker: complaints of "gas in the stomach," belching, a sense of fullness and distress coming on soon after meals; constipation of the spastic type; in three cases only, vomiting and severe pain. Headaches of the migraine type were second in frequency; asthma, in definite attacks, was third. Urticaria and eczema were seen a few times; vasomotor rhinitis from an identified food only twice.

In diagnosing these food sensitivities and separating them from the digestive disturbances incident on the one hand to the toxemia of tuberculosis, and on the other to organic disease (usually tuberculosis) of the gastrointestinal tract, skin tests were useful in about half of the cases. When all food tests were negative and the symptoms still pointed to sensitization, trial diets were employed for diagnosis. These diets, patterned after those of Rowe [3] but enriched by the addition of foods which the patient had seldom or never eaten, were highly effective in the difficult cases, not only in diagnosis but in treatment.

As is not uncommon, the symptoms set up by food sensitivity in two cases simulated those of non-tuberculous disease within the abdomen. In one, the picture was almost that of recurrent appendicitis except that the

blood examination revealed, instead of a leukocytosis, a normal white count with an eosinophilia. Another patient had for a year before admission been treated for cholecystitis. The barium meal with visualization of the gall-bladder showed no abnormality, and the symptoms ceased when wheat was excluded from the diet.

Even the barium meal was misleading in the following case, cited because one of its roentgenograms, reproduced in figure 1, constitutes one of the few existing photographic records of edematous lesions of the gastric mucosa caused by an identified atopen.

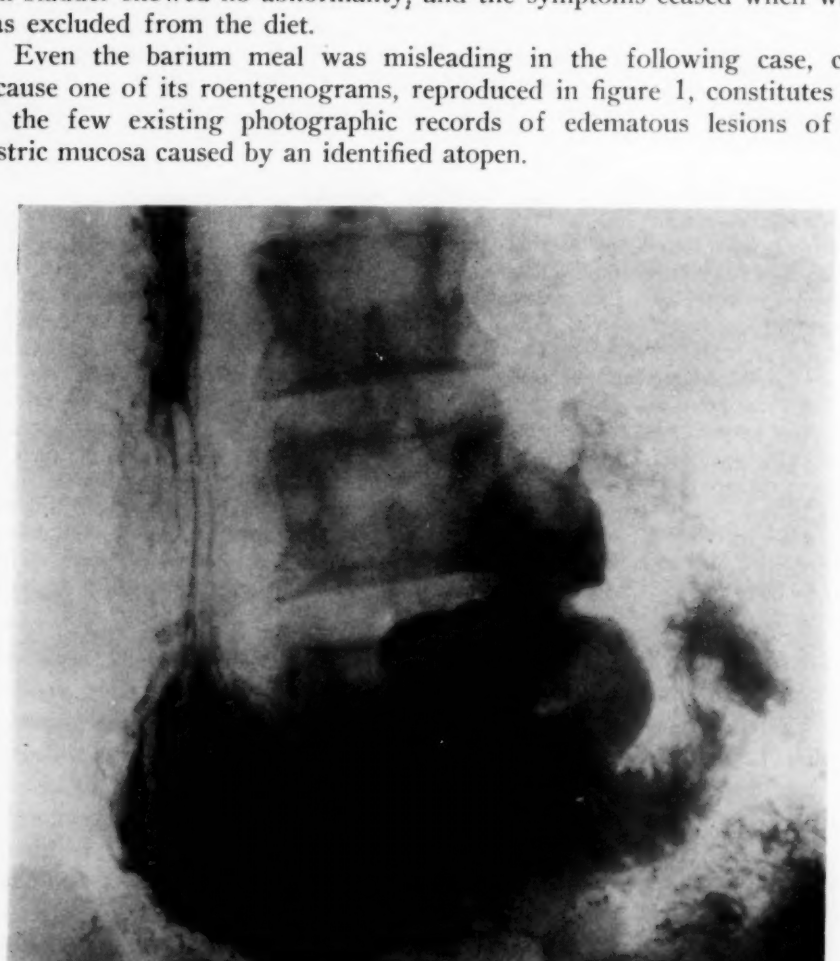

FIG. 1. Roentgen-ray of stomach showing filling defects due probably to edematous areas in the gastric mucosa, atopic in origin.

Case 2. F. S., a young married woman, never pregnant, was admitted for the treatment of fairly recent tuberculosis of moderate extent. She was questioned in detail as to the presence of atopic disease in her family, and denied it. She said her own health had always been good, except for constipation. She was put on routine rest, and cod liver oil in tomato juice was ordered.

The girl was homesick, and she disliked the restrictions of the rest cure. After a week she began to vomit all her meals. For a few days she did fairly well on a diet of broth, milk, and carbonated water. Then her vomiting recurred, and with it violent abdominal pain, and retching. She could keep nothing on her stomach;

spasms of pain and retching kept her awake at night. All the usual palliative medication, including sedatives, and belladonna to its physiologic effect, was tried without relief.

Her temperature was normal, her urine negative. A surgical consultant found no evidence of organic disease. A gastro-enterologist after careful examination was forced to the conclusion that a gastric neurosis was responsible for her symptoms. He ordered bromides and normal salt solution by rectum, with nothing but cracked ice by mouth, for two days. During those two days she was quiet, but when oral feeding was resumed her symptoms returned. Her condition was alarming, and her family was notified.

After several trials a barium meal was retained and the roentgenologist, Dr. W. W. Watkins, reported: "At the six-hour period the patient shows stomach incompletely emptied, with areas of filling defect. If these areas are not due to food taken into the stomach . . . they should call for a reëxamination. Two days later this was done, with the patient under constant observation to see that she took no food. The filling defects were again seen, and the report was: "We have reëxamined this patient, watching the barium enter the stomach with the patient standing. There are definite areas of filling defect which gradually disappear as the stomach partly fills with the barium mixture. These filling defects we believe were due to intragastric changes in the lining membrane of the stomach, probably polyps."

Then the family arrived, and it was learned that the patient's mother suffered from migraine and her two brothers had hay fever. It was recalled that her blood count, a few days after admission, had shown 3 per cent of eosinophiles—a hint that inexcusably had been ignored. Skin tests were done, and they revealed positive reactions to several foods, the strongest being tomato. Feeding was cautiously resumed with the implicated foods excluded. There was no further trouble, and the patient's subsequent course was uneventful. The roentgenographic picture three weeks later showed a normal stomach.

The offending foods were oftenest those which the patients had taken in excess in the hope of gaining weight: milk and egg, of course; cocoa, from the chocolate-flavored drinks advertised as body-builders; and tomato, from the vogue of tomato juice as a vehicle for cod liver oil. As in any series of food sensitizations, wheat, potato and chicken often reacted positively. Implicated foods were excluded from the diet until relief occurred; then, in most cases, they were fed again, one at a time, before being permanently forbidden. Sometimes in a multiple-sensitized patient a certain food, tried in this way, would cause the recurrence of one symptom only, and not the symptom-complex from which the patient formerly suffered. In the case of C. McD., for example, the addition of milk to the diet brought back the headaches to which she had been subject; the feeding of eggs caused asthma; wheat and white potato produced digestive disturbances, mild continuous wheezing and nasal congestion. When all these foods were eliminated from her diet the patient gained weight, and felt better than she had for years. Recently, after two years of abstinence from these foods, she tried them again, one at a time, and they had the same effect as formerly; this notwithstanding the fact that in the interval her tuberculosis had become arrested and she was leading a normal life at the time of the second experiment.

The four cases whose atopens could be identified only indirectly, al-

though they received a disproportionate amount of attention, may be disposed of quite briefly. All four had eosinophilia, a positive family history, and negative skin tests. One patient had vasomotor rhinitis and mild asthma, relieved by a staphylococcus filtrate. Another had intense and intractable asthma which disappeared, not to return up to the present (18 months), following the injection of a few doses of antuitrin. In both cases the treatment was probably nonspecific. The third, with persistent asthma, was relieved only while in the allergen-free room. It has not been possible to find the offending inhalant, and this patient has had no relief. The fourth, who suffered from classical migraine that had continued unaffected by all the usual methods of attack, experienced complete relief after six infected teeth were removed.

Eosinophilia and the Family History. An eosinophile count exceeding 2 per cent, and ranging from that up to 21 per cent, occurred in 32 of the 54 cases showing clinical evidence of sensitivity; it was present in only 27 of the remaining 196 cases, and one of these 27 has lately developed hay fever.

A family history of atopic disease was present in 32 of the 54 cases showing sensitivity, and in only 14 of the remaining 196 cases. Of this group of 14, one patient later died in an asthmatic seizure; two others developed hay fever.

The combination of positive family history and eosinophilia occurred in 23 of the 54 atopics, and only six times in the remaining 196 cases. Of these six, one now has orris coryza, and two children of another are asthmatic. It is clear that in this group of chronic tuberculosis patients the occurrence of eosinophilia (higher during exposure to the offending protein), the history of a familial trend to sensitivity, and still more the combination of the two, were of value in pointing to the probability of sensitization to foreign protein.

Comment

Estimates of the frequency of occurrence of atopic manifestations among the general populace vary all the way from the conventional "about 1 per cent" to Rowe's [3] estimate of 35 per cent in a group of 400 university students, and Vaughan's [4] appraisal, also based on anamnestic data, of 10 per cent of major allergy and 50 per cent of minor allergy in a group of 508 persons. That sensitivity to foreign proteins, especially to pollens, occurs often among tuberculosis patients in the Southwest has been noted by several workers in that region, including the writer. Sherman and Egbert [5] in a recent publication comment upon it, and attempt to explain its mechanism. Their thesis, if I understand it, is that the constant absorption of tuberculotoxin produces in the patient not only a relative immunity thereto, but also an allergic or "supra-allergic" state, in which sensitivity to foreign protein is more readily acquired. Quoting from their paper, "If we consider this

condition as the assimilation of a foreign protein into the tissue cells in such a state that the cellular activity is impaired with resulting edema then the so-called allergic individual may exhibit his symptoms in numerous devious ways. Too, once a patient exhibits any of these phenomena his blood-plasma is so changed that he soon acquires other foreign proteins which acquisition may progress until the original inciting cause is lost in a maze of allergic symptoms."

It seems unnecessary to venture so far afield to find an explanation for the prevalence of acquired sensitizations among the tuberculous; not in this series, at any rate. Most of the patients had chronic tuberculosis; all were on the rest cure, and they spent nearly all of their time in the open air. And in the region in which they were living, as I have shown in earlier publications,[6] exposure to pollen is considerable. Fertile soil, a warm dry climate and abundant irrigation favor a rank vegetation, much of which is wind pollinated. There is little rain, and pollen remains a long time in the air and still longer in the dust. The pollinating season is nine months long, and in protected places plants bloom sparingly in the three remaining months. With so adequate an exposure it is not surprising that patients who have inherited the capacity to become sensitive to inhaled protein-bearing particles should develop pollenosis. But the pollen burden of the air in the Southwest, as shown by Durham's[7] surveys, is less than that which occurs in the eastern and central states during the hay fever seasons—the very months when tuberculosis patients are most in the open air. It may be that careful investigation among such patients would reveal unsuspected cases of pollenosis, especially of the atypical sort described earlier in this report.

An equally simple reason for the prevalence of food sensitivity among tuberculosis patients suggests itself. The chronic chest patient leads a monotonous life. Food becomes a major interest, meal time an event in his day. Desiring to gain weight, he tends to overeat; and, since more than he can eat is set before him, he consumes in excess those foods which he likes or which he believes are good for him. His digestive powers being weakened by the enforced lack of exercise, probably at times he absorbs unchanged the proteins of his favorite foods. Under such conditions the mechanism of sensitization is rather obvious.

The present study does not corroborate the finding of Sherman and Egbert that "acquired allergy is most prevalent in arresting cases of tuberculosis, in which the immunity is greatest." All but nine of the 54 patients with clinical manifestations of sensitivity had active tuberculosis and positive sputum at the time their atopic symptoms were diagnosed. Several others (four, to be exact), as previously noted, developed sensitizations later in their course, and three of these still had active tuberculosis. But at least as many others lost their clinical reaction to foreign protein while their tuberculosis was healing, which is what occurs in any group of atopic persons, whether sound or tuberculous, if they receive appropriate

treatment. It is suggested that if in a group of tuberculosis patients acquired allergy (in the limited sense) is found oftenest among those with healed or healing disease, it is because such patients have been longer on the rest cure, and so longer exposed to some particular foreign protein.

While the effect of sensitization episodes on the clinical course of tuberculosis varied with the reaction-type, they all had one feature in common —discomfort. In chronic cases of the sort here considered, with extensive disease and many conditions influencing the physical state, one hesitates to evaluate precisely the effect of intercurrent ailments, or of their treatment. Of the pollen cases in general it can be said that, following the control of their pollenosis by adequate therapy, they were more comfortable and felt better. While I have seen a few cases in which the larger doses of a preseasonal pollen course produced a tuberculin-like effect in the presence of active tuberculosis, this has not occurred when the low dosage intradermal method was used. This statement includes the one patient of this series who had a sharp constitutional reaction ("pollen shock") early in her treatment. Lichtenstein [8] even administered pollen extract intravenously to a consumptive without apparent detriment. Sherman and Egbert find that desensitization of a tuberculous individual to an offending protein is harmless. It may be said that it is worth while to protect the tuberculous invalid against the discomforts of pollenosis of either type. Such desensitization is safer than to permit the pollenosis, with its attendant risk of sinus infection, to continue; and it can be accomplished as well during the attack as at any other time, if the proper methods are used.

Sensitivity to foods caused not only discomfort but also some impairment of nutrition. Not only patients whose symptoms were referred mainly to the digestive organs showed this effect; those with migraine and asthma lost weight when the seizures were frequent. Correction of the diet in such cases was always beneficial to the general health, and to that extent at least it aided recovery from tuberculosis. The working rule that restriction of diet should never be carried to the point where it caused a continuing loss of weight was found to be important. If necessary, dextrose was used to add extra calories to the trial diets. As a matter of fact, most of these patients gained weight when relieved of the distress caused by specifically offending foods.

The study of so many individuals from the viewpoint of the allergist consumed considerable time, effort, and material; but considering the results obtained and the period of time over which these results were helpful to the patients concerned, the undertaking has seemed worth while, and worth continuing as a part of institutional routine. Pollen-sensitized patients were relieved of discomfort which interfered with their rest. Those sensitized to foods not only were made more comfortable, but their nutritional state was improved; a few were freed from disturbances which threatened the success of their entire treatment. It is not suggested that work of this sort is a prime requisite in the successful treatment of tuberculosis; too

many have recovered without it. But, taking a comprehensive view of the measures at the disposal of the clinician, it may reasonably be asserted that informed attention to the diagnosis and treatment of sensitivity as it occurs among chronic tuberculosis patients will be helpful to a considerable number of these, and a useful addition to the hygienic treatment of tuberculosis.

Summary and Conclusions

1. Two hundred and fifty consecutive chronic tuberculosis patients were observed in an effort to determine the frequency and the effect of atopic disease among them. Fifty patients, one-fifth of the total, presented clinical evidence of sensitization to identified foreign proteins.

2. Thirty-four of these atopic patients were pollen-sensitive. About half of these had simple hay fever, easily controlled by specific therapy.

3. The remaining pollen-sensitive patients presented the atypical symptoms of increased cough and increased expectoration. These symptoms were likewise controlled by pollen therapy.

4. Sensitivity to foods alone occurred in about one-third of the atopic patients. Some of the pollen-sensitive reacted to foods as well.

5. The symptoms of food sensitivity resembled frequently the digestive disturbances incident to the toxemia of tuberculosis; less often, those caused by organic disease of the digestive tract. Both sorts were relieved by exclusion of the offending foods from the diet.

6. The discomfort incident to pollenosis interfered with the patients' rest and was detrimental to their general health. Food sensitivity, in addition to this, impaired their nutritional state.

7. In dealing with food sensitivity in tuberculous patients, the diet should not be restricted to the point of causing continued loss of weight.

8. Chronic tuberculosis patients on the rest cure, spending most of their days and nights in the open air, are heavily exposed to pollen in the pollinating seasons.

9. The same patients, leading a monotonous life and desiring to gain weight, are likely to eat in excess foods such as milk and egg, and tend to become sensitized thereto.

10. Appropriate pollen therapy, before or during the attack, may safely be employed in the presence of active tuberculosis.

11. The recognition and proper management of sensitivity to foreign proteins constitute a useful addition to the hygienic treatment of tuberculosis.

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PAIN—THE PATIENT'S COMPLAINT *

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PAIN is defined in Dorland's Medical Dictionary as "distress or suffering." The derivation of the word is from the Greek appellation for penalty. Hence, in Webster's Dictionary, the first definition is given as "punishment, penalty, or fine," and its common usage as "an affection or feeling due to derangement of functions, disease or bodily injury," second, and "distressing uneasiness of mind; grief" is placed fourth.

With consideration of the wider uses of the word "pain," practically all bodily and mental ills present attributes which may be included under this designation. Pain is the most frequent complaint offered by the patient when he consults the physician. With the wide scope allowed by the definition and the innumerable conditions which give rise to painful sensations the complaint obviously requires limitation and careful investigation.

VARIETIES OF SENSATION DESIGNATED AS PAINFUL AND SOME MECHANISMS INVOLVED

Pain is a necessary part of an animal's mechanism of defense—the automatic danger signal. But perception of painful stimuli varies greatly, for it is bound up with the patient's physiological functions and emotional stability. Various areas and organs of the body do not respond equally and in the same manner to stimuli.

Illustrative of this physiological difference Lennander and Mackenzie's investigations showed that viscera do not respond to the same character of stimuli that give pain in somatic structures; viscera could be cut, pinched and burned without pain, the nerves supplying them not having the same property of pain conduction. Head established that the afferent visceral nerves were the same which furnished skeletal tissues with deep and protopathic sensibility. In the absence of the inhibition of the higher centers an impulse might be transmitted to the thalamus and cortex where pain is not ascribed to the particular viscus in which the impulse arises, but is referred partly to the surface of the body, as segments or sections are represented centrally, just as in the cortical motor system, movements and not muscles are represented. When painful visceral stimuli reach the perceptive brain centers the effect is regularly redistributed segmentally as definitely as motor and trophic distribution is accomplished in the cord. Each viscus supply is from several segments, hence, the area of reference may be widespread as particularly pointed out by Pottenger. Also Behan suggests impulses may travel up or down segmentally, before entering the central nervous system and then be reflected peripherally, giving referred pain. Head's law

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also offers a further criterion. When a painful stimulus is applied to a part of low sensibility in close central connection with a part of much greater sensibility, the pain produced is felt in the part of higher sensibility.

As expressed in the definition, the complaint of pain does not preclude that a true physiological sensation of pain is present. The complaint called painful may result from irritation due to distention of a hollow viscus, from reflex spasm of a neighboring organ, may present itself peripherally as a tender or painful point or arise from innumerable stimuli. It may be expressed in any form of sensory appreciation, as an actual sense of pain, hyperalgesia; or hypalgesia; abnormal heat and cold sensation; irritative phenomena, felt as tingling, scratching, formication, gnawing, electric-like; a feeling of pressure, or weight pulling, stretching, soreness, aching, or any known sensory perception, its description usually being influenced by the patient's intelligence, experience and education.

Furthermore, differentiation between sensitiveness and tolerance must be made. Libman uses as a test for individual sensibility, pressure against the tip of the mastoid and then over the styloid process. He quotes Sir James Paget in that "pain expected, watched for, long thought of, will come" and calls attention to the recognition of the factor and effect of distraction. He also points out the existence of covered symptoms in the hyposensitive individual where pain is not predominant, as the dyspnea of coronary disease overshadowing precordial distress which might be marked in the absence of dyspnea.

In multiple foci of a disease, change of position allowing another pain point to cover one previously distressing, is a common observation. One condition of two different clinical entities may not be noted in the presence of one more distressing and important, as an arthritic pain in the presence of angina. Substitution symptoms occur frequently, as the complaint of fullness, pressure, gas, headache, etc., in the presence of gastric ulcer. Hyposensitive individuals may dread dental drilling more than extractions and in this type advanced neoplasms may give referred and substitution symptoms of "crowding," pressure and vague discomforts which must be magnified in estimation of the true condition.

In this general but great difference in the reactions to pain between the sensitive and hyposensitive, it appears that the impulses travel more directly to the central nervous system in the former while in the hyposensitive impulses seem to be delayed in the autonomic system.

Carnett refutes the viscero sensory reflex viewpoint, believing that much lower abdominal pain is parietal neuralgia which his skin pinch test will differentiate from intra-abdominal pathology and thus obviate much misdiagnosis and unnecessary abdominal surgery.

Physiological nerve function, though somewhat complex and confusing at times, is usually given appropriate consideration and study, but the rôle of neurotic tendencies and frank psychoneuroses in the causation of physical disability is not fully appreciated. Their presence and manifestations,

however, may be fully as distressing as any physical discomfort. All ailments and physical incapacities are influenced by the attitude of the patient toward them. When this attitude is dictated by an unstable emotional system, mental conflict and ungratified wish fulfillment, the symptoms presented are variable, confused, complicated and perplexing. Hence, routinely, this attitude must always be considered if one is to expect complete and rapid recovery from the condition present, and when the situation is complicated by the presence of a psychoneurosis it is extremely helpful and often necessary to evaluate its influence properly.

To best accomplish this, a workable understanding of the mechanisms involved in psychogenic symptom formation is as necessary as knowledge of the pathological and physiological processes involved.

Hysteria is the most protean and varied of mental disorders. Its psychology includes opposing wishes with accompanying mental conflict which often manifests itself in bizarre behavior in the attempt to influence spectators and auditors.

Frequently associated are sexual desires striving for satisfaction against opposing inhibitions of fear-dominated conscience. Usually conscience wins in the conflict but whatever the result disappointment and dissatisfaction ensue, leaving little chance for happiness in the hysteric. Usually emotionalism with temper outbursts appear or unconscious compromise by symptom development serves to gratify repressed desires by substitution or symbolism. These subconsciously motivated symptoms may take the form of a phobia, a tic, an illness or somatic reference to any organ or system. This may offer a solution for the mental conflict, but its subconscious motivation not being recognized, relief is sought for this very symptom which is the gratification of the consciously intolerable wish. The substitution in this way of physical symptoms for emotional problems constitutes "conversion hysteria." Here emotional energy instead of appearing in higher behavior levels as intellectual and mental activity seems to be resolved by the development of physical symptoms through neural transmission paths in the form of more obvious physical and motor manifestations. This mechanism is responsible for many of the minor disorders in general practice. The symptoms presented are probably not desired as such, either consciously or subconsciously, but they are purposive, in that they serve as a means towards the desired end or goal.

Economic hardships and social demands make wish fulfillment difficult to achieve. The liability to physical impairment is thus obviously increased, offering a very definite economic as well as medical problem, as shown by the development of increased incapacity in employees and in the insured and in a marked increase in the number of indigents requiring charitable aid.

Such somatic conversion of symptoms may involve any bodily organ but the genital and erotogenic zones are particularly prone to be the sites involved. Irrespective of the particular complaint offered in this condition the underlying mental conflict is usually quite obvious and causative of much painful distress.

Without proper supervision this distressed patient seeks aid promiscuously, frequently becoming the victim of quackery and of mercenary, unethical individuals who only more firmly fix his symptoms and, incidentally, usually relieve him of his available funds and assets. On the other hand he may be conscientiously treated by ethical and well trained physicians who are not sufficiently familiar with or cognizant of the syndrome or mechanism in the development of the bizarre unrelated manifestations which may be presented.

Patients with conversion symptoms are seen in all specialties of medical practice but due to the fact that the most frequent zone of reference is that of the sexual and neighboring organs, the gynecologist, urologist, gastroenterologist and proctologist are most likely to be sought for advice or treatment.

A few examples of symptoms developed in this condition demonstrate its mechanism.

Case 1. C. Y., 30, bank clerk, contracted gonorrhea from the girl he had planned to marry, which offered more emotional distress than physical, for many months. However, about two years later he married another girl, who during her pregnancy which began the first month of their married life, was sick much of the time, had a very arduous and dangerous labor, and following the birth of the child gave it intensive attention with little to the husband. Fear of another pregnancy possibly further lessened her limited sexual desires, and gave the husband need for long continued repression. During this time economic stresses in the form of salary decreases and the wife's parents moving in with them, aided in the development of an anxiety neurosis. After a few weeks of intense worry and some emotionalism the patient developed a severe pain in the anal region relieved only by standing. He found himself unable to sit at his desk for more than a few minutes at a time and frequently at bedtime or during the night he was impelled to arise and gain relief by walking. He consulted an able urologist who treated him with prostatic massage and finally, as the symptoms did not abate, resorted to a prostatic median bar transurethral resection, which was also ineffectual. He was then advised to have a rectal examination in search for the causative source. A minor rectal operation was advised and accepted without relief. Meanwhile he had had several negative physical examinations and was found upon neurological examination to have no organic disease of the nervous system.

Case 2. J. S., 43, electrician, was referred by a proctologist to whom the patient had been sent by a urologist, with an identical complaint of rectal pain. Their examinations disclosed no genito-urinary or rectal lesions. Only a few details in his long search for relief will be mentioned. At 19 he had contracted gonorrhea from which he quickly recovered but, thinking treatment should be continued, he left his parents' home and came several hundred miles to live in Los Angeles, among strangers and for a year continued unnecessary treatment with advertising specialists. Then called to army service he apparently adjusted well and obtained a good position upon discharge. Four years ago, however, rectal pain suddenly began and has continued since, causing much loss of sleep, inability to hold a position, psychic impotence with its attributes added to his anxiety and emotionalism, the treatment of which had dissipated his resources, due to his persistent search for relief. Throughout his trouble he received no examination or treatment from ethical physicians until examined last month by the urologist and proctologist mentioned. He spent $750.00 for a goat gland bilateral testicular transplantation but the pain recurred promptly

after the operation. He had also paid $150.00, cash in advance, for glandular extract injections, and several hundreds more of his frugal savings with advertising "men's specialists."

Case 3. C. W., 21, broker's clerk, was referred by a urologist who recognized his complaints of numbness of the penis, psychic impotence, extreme lassitude and apathy as psychogenic in origin. Subconsciously he had built on fear, shame and a feeling of inferiority following a gonorrheal infection over a year previously. A personality change from that of an active social individual, efficient in his work to one of inactivity, isolation, indolence, lack of interest, impaired integration and inability to concentrate had occurred. He avoided all his former friends and social gatherings but was retained in his position for a time, in spite of his attitude, by an understanding and patient superior.

Case 4. Mrs. A. C., 26, was referred by a urologist to whom she had been sent by a friend to discover if any physical reason existed for absence of sexual gratification at intercourse and persistent dysuria and frequency. Her entire girlhood had been embittered by the constant argument, harangue and bickering between her impatient, hypercritical, quarrelsome parents. After disappointment in a matrimonial engagement to a man near her age, she was much distressed and very emotional for over a year. Near the end of this period she became acquainted with a man almost 30 years her senior, who was very understanding and patient with her mental turmoil and distress. This man fulfilled the father ideal which she had entirely missed in her own father, as well as fitting the rôle of lover. Marriage ensued yet, despite frank discussion of both the physical and mental phases of sex in married life, physical difficulties and economic stress led to increasing marital estrangement.

Physically the patient was extremely well developed and likely oversexed. This, together with obvious failure of gratification, early in her married life, due to partial impotence in her husband, caused her the definite physical distress of unrelieved desire with increasing repugnance towards her husband. Psychic frigidity developed and conversion symptoms in the form of dysuria and frequency appeared. Divorce was seriously contemplated and extreme unhappiness was being experienced by an intelligent and otherwise coöperative and congenial couple.

Case 5. Mrs. J. S., 26, gave nearly an identical history except that she had married a man near her age. She had consulted a female osteopath who had attributed all her trouble to uterine retroversion. Many months' treatments with packs, pessaries and position exercises had but further increased the patient's dissatisfaction until the very presence of her husband brought on emotional episodes very disastrous to marital peace and happiness.

Case 6. Miss G., 28, a hard-working office woman, the sole support of her invalid mother, had lived an extremely restricted social life, giving all her time outside of working hours to the care and entertainment of a selfish, demanding and critical mother. A gastrointestinal upset caused her physician to suspect a mild attack of appendicitis.

Within the next two years similar attacks recurred every few weeks, which resulted several times in hospitalization, careful study and consultations. An element of exhibitionism being present also, the attention she received while ill brought no little satisfaction and gratification into her emotionally starved and limited existence.

Case 7. A 17-year-old high school boy was taken to the ophthalmologist because of rapidly failing vision. Vision was found to be 6/6 in each eye and no pathologic lesions were present except a mild traumatic *blepharitis marginalis.* The history was given that the boy had not resumed school four months previously at the opening of the session, apparently on account of his inability to see well enough to study. Upon examining the boy a first degree hypospadius was found present. Further investigation revealed that he had attempted to avoid his fellows and isolate himself, for

they were considered "normal," "able" and physically maturing as he was unable to do, completely, on account of his physical impairment. A feeling of inferiority, inadequacy, shame and much mental turmoil had developed. Subconsciously the conversion symptom most effectually removing him from his disturbing environment developed in the form of marked visual impairment. School attendance was obviated and association with his normal companions was much restricted.

In this situation much difficulty would be experienced by this patient in properly adapting himself, with the ideas he held regarding the extent of his physical inadequacy. Consequently a plastic operation was advised but the physical impairment and its attributes were minimized to him, awaiting the acceptance and results of the proposed operative procedure.

Diagnosis of Psychoneurosis

Similar conditions could be recited tiresomely. Daily, puzzling syndromes, complicated by the patients' emotional content or actual psychoneurotic manifestations, are presented to the examining physician. Frequently the underlying motives are obvious but at other times the psychic element is extremely difficult to evaluate. Whenever the subjective complaint is not accompanied by definite physical conditions and signs which might reasonably be the exciting causes, the social, economic and emotional states of the patient should be investigated. Rather than by a process of exclusion, however, the symptomatology of the psychoneuroses should be as readily recognized as that of other illnesses. There is usually present a demonstrably peculiar emotional state of abnormal suggestibility. There is frequently a tendency to blame the medicine prescribed or the therapeutic measures instituted for continuance or exacerbation of symptoms. Often this resentment is extended to the physician who has suggested the specific remedial agents and the tendency to blame anyone but himself for his condition, physical, economic, and social is usually present. The patient's past history usually evidences ineffectiveness in his personality, poor adaptation to his environment, inadequate handling of his personal problems, often disagreements with his confrères and superiors, which may cause frequent changes in positions and abodes, social difficulties or marital infelicity and general maladaptation and frequent errors in basic judgment throughout his life. The elicitation of faulty thinking, mental conflict or unusual reactions must be given their proper degree of importance in the study of the patient and his complaint.

Furthermore, the psychic reactions to every illness or disability play an important part in its degree of incapacitation, progress and treatment.

The patient's sum of past experiences, economic and marital status, emotional stability, ease of adaptation to varying situations, personality type and degree of happiness at the time are but a few of the numerous contributing factors influencing this reaction. Hence, in the emotionally unstable, worrisome, highly suggestible individual, it is often more efficacious and productive of greater final good to minimize the effect and danger of benign, innocuous, nonprogressive conditions, or postpone their treatment,

if it can be done without risk, until the patient's mental turmoil, anxiety and introspection become lessened.

Treatment

The treatment of an existing psychoneurosis consists principally in reëducation in a new attitude towards life and its problems. In an older resistive person whose opinions, thinking habits and reactions are fixed a real problem is presented but usually a better adjustment can be affected. Fundamentally the confidence of an introspective, egotistical, self-centered individual, in which type such conditions usually exist, must be gained. If practical, in the particular patient, explanation of the mental mechanisms in the development of his symptoms may be helpful. In a patient where this method would be inadvisable or poorly understood, material obvious agents, in the form of physical therapy and electrotherapy, may be helpful, using care they are not accepted as panaceas.

Tactful, indirect suggestion, encouragement, incentive for recovery and a better method of reaching desired goals need to be offered. A transfer and diffusion of interests will need to be developed by encouraging physical, intellectual and social activities, pointing out the obvious compensations that they offer.

Withal, a more philosophic and optimistic attitude must be promoted and methods of better adaptation demonstrated.

Neuropsychiatrists have been accused, at times, of being impractical, visionary and, what is still more important, of neglecting possible physical attributes in conditions presented for their investigation. Many medical practitioners, especially those in special work, are liable to become limited in their viewpoint. Fortunately these tendencies have been much lessened with the more intensive medical training in all basic branches of practice in school, hospital and graduate study. With the development of greatly broadened viewpoints generally, the neuropsychiatrist is able to point out to his confrères that the damage accruing from over enthusiastic, injudiciously applied, diagnostic and therapeutic measures may be as great in the suggestion and fixation of ideas and the development of a neurosis as their benefit may be obvious when they are indicated.

The value of considering the patient's reaction to his ailment cannot be overestimated. Consequently, knowledge helpful in the estimation of its effect and evaluation is as necessary as that regarding other investigative procedures. Palliative treatment may alleviate the acute distress by removing obvious physical evidences of discomfort and incapacity. However, when the symptoms are of psychogenic origin, or a condition is exaggerated, prolonged and made more materially incapacitating by the subconscious mental reaction towards the symptoms, an intensive reëducational procedure needs to be employed. With this accomplished the patient will learn to live the happy, contented existence to which he is entitled.

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THE ASSOCIATION OF POLYCYTHEMIA VERA AND PEPTIC ULCER *

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OUR interest was aroused in the significance of the association of duodenal ulcer and polycythemia vera as a result of observation of a patient who had both diseases. A review of the literature revealed interesting speculations in regard to the association of these conditions because of recent demonstrations of the relation of gastric secretion and hematopoietic function. It seemed reasonable that with the large amount of material available at this clinic some conclusions might be drawn as to the incidence of association of these diseases.

In the available medical textbooks, the gastrointestinal symptoms associated with polycythemia vera are minimized. Osler [1] dismissed the subject with the simple statement, "Gastrointestinal symptoms are not prominent." Perhaps the most common manifestation referable to the alimentary tract of patients with polycythemia vera is constipation, which is variously described as being inconstant or common. The next most frequent abdominal symptom usually is distention or fullness, which is usually explained on a basis of pressure exerted by an enlarged spleen; it is sometimes accompanied by pain, which is often localized in the epigastrium or left upper quadrant of the abdomen. Nausea, vomiting, and anorexia occur quite frequently. Melena or hematemesis may occur, as may epistaxis, hematuria, menorrhagia, cerebral hemorrhage, or bleeding into the pleural cavity.

The first report of the association of the two diseases was in 1905, thirteen years after Vaquez [2] described polycythemia vera. In that year Weber and Watson [3] reported observation of a patient who had polycythemia vera and who gave a history suggestive of peptic ulcer. At necropsy there was observed an intense congestion of the gastric mucosa and a round ulcer on the posterior surface of the stomach, 2 inches (5 cm.) from the pylorus. Schneider,[4] in 1907, reported the simultaneous occurrence of gastric ulcer and polycythemia vera. Giffin [5] has also noted the occasional association of peptic ulcer and polycythemia vera.

In 1913 Friedman [6] advanced the opinion that duodenal ulcer might be a trophic disorder due fundamentally to a disturbance in the secretion of epinephrine, which he suggested as the cause of the polycythemia in the cases he had observed. He stated that polycythemia is apparently a frequent finding in cases of duodenal ulcers that do not bleed, and that this is not true of gastric ulcers. In most of his cases the existence of duodenal ulcer had not been proved, and in many cases polycythemia was probably of

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a secondary or concentration type. In 1914 Friedman [7] reported the occurrence of an elevated erythrocyte count in 13 of 16 cases of duodenal ulcer, and observed that the polycythemia continued after operation in those cases in which surgical treatment was undertaken.

Naegeli,[8] in 1919, mentioned pyloric ulcer with obstruction as a cause of relative or concentration polycythemia. Bing,[9] in 1920, reported two cases of duodenal ulcer associated with polycythemia, and stated that Danish writers had observed four similar cases. He was of the opinion that the polycythemia was a result of three factors: gastric hypersecretion, delayed passage of food from the stomach, and dehydration from frequent vomiting. Hirschfeld,[10] in 1925, stated that the polycythemia which may be observed in pyloric stenosis occurs as a result of lessened fluid absorption.

Tuchfeld,[11] in 1931, observed that patients with pyloric or duodenal ulcers frequently have an associated, abnormally high erythrocyte count and hemoglobin value. He contrasted the anacidity associated with pernicious anemia with the hyperacidity observed in these cases of duodenal ulcer and polycythemia. He suggested that in the latter cases there is an excessive production of that component of the gastric secretion which is concerned with the formation of erythrocytes. Morris,[12] who named the hematopoietic factor of the gastric juice "addisin," suggested in 1933, as had Tuchfeld [11] previously, that in polycythemia there might be produced an excessive amount of this factor, in contrast to the lack of its production in pernicious anemia. He advised a patient who had polycythemia and a duodenal ulcer to lavage his stomach three or four nights a week for a period of six months. During that period the erythrocyte count dropped from 10,000,000 to 5,300,000 per cubic millimeter. When lavage was discontinued, the count again rose to 10,200,000. Recently, Oerting and Briggs [13] reported a favorable influence of gastric lavage on "familial and nonfamilial erythremia." These observers found, in addition, that the gastric secretions of patients with polycythemia were capable of producing remissions when placed untreated in the stomachs of patients with pernicious anemia.

Boyd,[14] in 1934, reported the simultaneous occurrence of polycythemia, leukocytosis, and duodenal ulcer. He called attention to the known tendency to thrombosis often observed in polycythemia vera, and offered the opinion that the duodenal ulcer was probably secondary to thrombosis in the duodenum.

Not all writers have been able to concur in the opinion that duodenal ulcer and polycythemia are frequently associated. Allodi and Griva,[15] in 1930, reported 63 cases of ulcerating or nonulcerating affections of the duodenum, or other sections of the intestine, accompanied by hyperchlorhydria. In only two cases was there actual elevation of the erythrocyte count.

It is important to recognize that some of the cases reported in the literature as polycythemia vera probably should not be classified as such in the absence of more definite criteria of the disease. Undoubtedly some of these patients presented concentration polycythemias or polycythemic hypovolemia,

and one must be cautious, therefore, in drawing too many conclusions from reports in the literature. The reports of several authors have raised interesting speculations as to the etiologic relationship between polycythemia vera and ulcer. It has been suggested that both diseases are a result of disturbance in the secretion of epinephrine, that polycythemia is relative or secondary to loss of fluid, that duodenal ulcer, being associated with hypersecretion, results in an excessive production of an intrinsic erythropoietic factor, and that the occurrence of ulcer is the result of thrombosis of vessels in the gastric or duodenal mucosa.

Cases Studied

We investigated 143 cases of proved polycythemia vera at The Mayo Clinic for the purpose of determining the frequency of associated peptic ulcer. The diagnosis of polycythemia vera was made in these cases on the basis of elevation of the erythrocyte count and hemoglobin content above normal values, increase in viscosity and volume of the blood, and a hematocrit reading indicating a higher percentage of erythrocytes than the normal value of 45 to 48 per cent. Many of the patients were observed over a considerable period, as they were under treatment with phenylhydrazine (Brown and Giffin,[16] Giffin and Allen [17]) and consequently the opportunity for detecting gastrointestinal symptoms was great. Of the patients, 114 gave no history suggesting the presence of gastrointestinal disease, and therefore had no roentgenologic examination. In 17 cases roentgenologic examination of the stomach and duodenum did not reveal any pathologic process; in 12 cases, or 8 per cent, there was roentgenologic or pathologic evidence of the presence of peptic ulcer.

In 10 of the cases of ulcer the lesion was in the duodenum, in two in the stomach. In the group of cases of duodenal ulcer, the lesion was demonstrated by roentgenologic examination in nine cases, at postmortem examination in one. In two cases of this group there were no features in the history to suggest the presence of peptic ulcer; in seven cases the history of ulcer antedated the development of symptoms or discovery of polycythemia vera by at least one year and in one case by 21 years. In one case there was some question as to the sequence, but symptoms of polycythemia vera were probably noted before those of duodenal ulcer. Six of the patients had symptoms of duodenal ulcer at the time of examination.

Of the two patients with gastric ulcer, one gave no history suggestive of ulcer, and the lesion was an incidental finding at postmortem examination. The other patient had symptoms of ulcer for four years, and of polycythemia vera for slightly more than two years.

Studies of the acidity of the contents of the stomach of patients with polycythemia are worthy of note in view of the possibility of a relationship between gastric secretion and polycythemia. In only one of 24 cases in which gastric contents were studied was marked hyperchlorhydria present.

This patient had an active duodenal ulcer, and the value for free hydrochloric acid was 80 units and for total acids (Ewald meal) 96 units. Four other patients with active duodenal ulcer had acid values moderately above those considered to be normal. Sixteen patients had acid values within normal limits, and four either had no free hydrochloric acid or very low acid values. In none of the cases without ulcer was hyperchlorhydria present. Unfortunately, studies of pepsin content of the gastric juice have not been made in most of these cases. In one case of duodenal ulcer and polycythemia vera in which the gastric pepsin was estimated following stimulation with histamine, the values were above normal, and were commensurate with the degree of hyperacidity. In another case of polycythemia vera without gastric or duodenal ulcer the pepsin values were two or three times the normal.

Comment

There are two points of interest in regard to this problem: first, whether there is a significance in the association of duodenal or gastric ulcer and polycythemia vera, and, second, whether there is a relationship, as suggested by Tuchfeld [11] and by Morris,[12] between changes in the gastric juice and the elevated erythrocyte count.

The actual incidence of peptic ulcer in the general population is unknown; studies by pathologists suggest that healed or active ulcers are found at postmortem examination in 10 to 20 per cent of cases. Hartman [18] reports that ulcer of the stomach or duodenum was found in 3.2 per cent of patients who registered at The Mayo Clinic in 1928. In a control series of 200 consecutive cases of hypertension, in which patients were examined in 1929, one of us [19] found the incidence of gastric or duodenal ulcer to be 2 per cent. In contrast with these control groups, the present study indicates that in 8 per cent of cases of definite polycythemia vera there was roentgenologic or pathologic evidence of peptic ulcer. Since not all of the patients with polycythemia vera were investigated to determine the presence of ulcer, and since in a few of the cases there was roentgenologic or pathologic evidence of the ulcer in the absence of symptoms suggesting ulcer, it is impossible to state accurately the exact percentage of association. While a duodenal or gastric ulcer was recognized more frequently in cases of polycythemia vera than in a control series consisting of patients with hypertension and the general clinic population, it is difficult to estimate the significance of this association.

It is possible that polycythemia vera belongs to a group of diseases including tumors of the brain and spinal cord, prostatic disease, chronic nephritis, chronic cholecystitis, and diseases of the thyroid gland, particularly toxic goiter, in which gastric and duodenal ulcer are apparently more commonly seen at necropsy than in other conditions.

Since there has been shown to be a direct relationship between secretion of certain constituents of the gastric juice and hematopoietic activity of the

bone marrow, there is much interest in the speculation that a disturbance in gastric function may be of importance in the development or continuance of polycythemia vera.

Tuchfeld [11] and Morris [12] have suggested the hypothesis that production of an excessive amount of hematopoietic factor may be responsible for increased formation of erythrocytes, and experience has shown that in some of these cases repeated loss of gastric juice by tube has resulted in a decrease in the erythrocyte count. Unfortunately, we do not know the exact relationship of the secretion by the stomach of acid and hematopoietic substances. It has been suggested that the secretion of one is independent of the other, and that in the absence of secretion of acid there may still be secretion of the blood-stimulating factor. On the other hand, we do not know that secretion of excessive amounts of acid also indicates that larger than normal amounts of the erythropoietic substance is also being secreted. If the latter is true, one could perhaps explain the apparently greater incidence of duodenal and gastric ulcer in polycythemia on the basis that the associated hyperacidity and hypersecretion in cases of ulcer indicated a greater secretion of erythropoietic substance and, therefore, more blood formation.

In the cases we have studied there has been little to support this hypothesis. There was no demonstrable evidence of secretion of large quantities of hydrochloric acid in the majority of our cases, and only moderate hyperchlorhydria in some of the cases with ulcer. On the other hand, the apparent occurrence of symptoms of ulcer antedating the onset of polycythemia in most of the cases studied by us might be considered supportive evidence. Subsequent studies should help in elucidating this problem.

We have no definite information regarding the relationship of thrombosis of the vessels of the duodenum to the development of duodenal ulcer among patients with polycythemia vera. There seems to be some merit in the hypothesis in view of the known tendency of polycythemic blood to form thrombi and the suggested relationship of vascular changes in the duodenum and stomach to the formation of peptic ulcer.

Summary

In 8 per cent of 142 cases of definite polycythemia vera there was roentgenologic or pathologic evidence of gastric or duodenal ulcer. In a control group of cases of hypertension and in the general clinic population the incidence of ulcer was 2.0 and 3.2 per cent, respectively.

It is pointed out that, with our present information, it is difficult to evaluate the significance of this association of diseases and that there is insufficient evidence to establish a distinct relationship between polycythemia vera and peptic ulcer.

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THE PRESENT STATUS OF THE PROBLEM OF "RHEUMATISM"; REVIEW OF RECENT AMERICAN AND ENGLISH LITERATURE ON "RHEUMATISM" AND ARTHRITIS *

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IN THREE PARTS

PART III †

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CHEMICAL AND ENDOCRINE ARTHRITIS

Under the term "chemical arthritides" can be conveniently grouped a number of joint diseases which are apparently closely related to chemical or metabolic alterations or to immunologic reactions. The forms of joint disease in which some chemical alteration (primary or secondary), or "chemical inflammation," seems to be the chief feature are gouty arthritis, arthritis of serum sickness, and hemophilic arthritis, to which list might be added intermittent hydrops, possibly an allergic arthritis from food, and ochronosis with alkaptonuria. Since the established endocrine disturbances are essentially chemical, a discussion of endocrine arthritis is included.

Endocrine Arthritis. The literature contains such terms as chronic thyroidal rheumatism, arthritis thyreopriva, endocrine or hypoglandular arthritis, climacteric or menopausal arthritis, arthritis ovariopriva, and polyarthritis acromegalia. Some are now attempting to launch "parathyroid

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arthritis." In any consideration of the endocrine glands and arthritis a definite distinction must be made as to whether the supposed endocrine disturbance is regarded as the sole or chief cause of the type of arthritis under discussion, or whether it is looked upon merely as a predisposing or aggravating factor of an arthritis primarily not endocrine. Certain endocrine relationships have been noted in both atrophic and hypertrophic arthritis, occasional alterations in metabolic rate being the most concrete examples. Almost every ductless gland has been suspected of being the cause of arthritis, but the thyroid and ovaries are suspected most often. There are sharp divisions of opinion as to whether an entity such as climacteric arthritis or any other form of "endocrine arthritis" really exists.[388] Saxon[389] and Jezierski (1931) favor the existence of such an entity. Saxon cites the usual arguments: frequent coincidence of menopause and hypertrophic arthritis, occasional lowered metabolic rate in both types, prevalence of arthritis where goiter is endemic, supposed benefits of endocrine therapy or pelvic diathermy, and so on. He found a lowered metabolic rate in about 50 per cent of an unstated number of cases of chronic arthritis, but thyroid medication only helped those patients who were obese or had signs of hypothyroidism. Ovarian therapy was not successful. Jezierski urges the use of Abderhalden's method and the interferiometric test to uncover endocrine arthropathy, which he describes as painful creaking, without much exudation, in knees especially but in other joints also. The use of oöphorin tablets, follicular injections, or soluble ovarian extracts is recommended, and massage and radiotherapy are not indicated.

Arthritis and Parathyroidism. It has recently been suggested that patients with parathyroidism frequently demonstrate arthritis, that at least in certain cases of arthritis, especially "ankylosing spondylitis" or polyarthritis, there are signs of parathyroidism and that the arthritis may be due thereto, and that in such cases parathyroidectomy gives relief (Ssmarin (1928), Oppel (1929), Taddei (1929), Leriche and Jung (1930, 1931), Simon (1931), Simon and Jung (1931), Ballin and Morse (1931)). Others have denied such relationships. The argument has been continued, with Funsten[390] and Ballin[391] in favor of, and Bauer,[392] Compere[393] and Nachlas[394] against, the proposition.

Among 95 patients with "arthritis, chiefly of the ankylosing type" Funsten noted 24 whose symptoms were suggestive of parathyroidism. The values of serum calcium were intermittently elevated. Parathyroidectomy was performed by Ballin in 14 of Funsten's cases. All but one patient improved (9 markedly, 4 moderately) within 4 to 18 months.

Bauer, Compere, and Nachlas protested, as did Welti (1931) and Lievre (1932), against the adulteration of the syndrome of parathyroidism with arthritis. They conclude that there is no clinical, chemical, or pathologic evidence of any relationship. No evidence of true arthritis was found in seven cases of proved parathyroidism seen by Bauer (in one case even after 13 years of parathyroidism), or in more than 50 proved cases reviewed by

Compere. No negative calcium balance was found in any case of arthritis of either the hypertrophic or atrophic type. In provable parathyroidism, the serum calcium is permanently, not intermittently, elevated. In none of the cases of supposed parathyroid arthritis were full metabolism studies carried out, and in no instance was a definite adenoma found at operation. Such relief as was obtained by parathyroidectomy must have been nonspecific, as after almost any procedure involving anesthesia and rest. Johnson [395] readily produced experimental parathyroidism and the picture of osteitis fibrosa cystica in animals, but arthritis was not evident. There is thus no justification for parathyroidectomy for arthritis and no proved connection between arthritis and parathyroidism.

Conclusions on "Endocrine Arthritis." While it is apparent that alterations in endocrine function may prepare the soil for, or may aggravate an existing, atrophic or hypertrophic arthritis, it is obvious that no convincing proof exists as to any primary endocrine arthritis. In acromegaly and in parathyroidism, the lesions are chiefly in bone. Secondary and relatively minor changes may become evident in joints, but "true arthritis" is not a feature. Neither atrophic nor hypertrophic arthritis is proved to be primarily endocrine in origin, nor is any other type of arthritis, for that matter, in the sense that the administration of a known endocrine product or the removal of a ductless gland is followed by unqualified improvement or cure comparable to the use of insulin in diabetes, removal of the thyroid in hyperthyroidism, or use of thyroid extract in myxedema. The closest that the disputants have come to agreeing on an "endocrine arthropathy" is in the cases of "villous arthritis," which others insist is not essentially an arthritis but a dry, proliferative, fibrous or villous synovitis. Even here, convincing clinical, pathologic, and therapeutic proof is almost entirely lacking. (To one of us [Hench], the most likely candidates for such a title would seem to be gout and hemophilic arthritis. Both are strikingly sex-linked. Metabolic or chemical alterations are their chief feature, and recent experience in medicine suggests that "metabolic" or chemical diseases are frequently being proved to be endocrine. Proof that gouty and hemophilic arthritis should be called endocrine awaits future studies.—Ed.)

Gout and Gouty Arthritis. Gout is a unique disease. Its ancestry can be traced back to the beginnings of recorded medicine. Its genealogy is most distinguished: no disease has a more noble pedigree or has enjoyed more regal patronage. Its drama unfolds with spectacular abruptness. Its violent torments may continue with a degree of pain which approaches the most agonizing in human experience, at times challenging all endurance. But in spite of these arresting attributes, gout, "the king of diseases and the disease of kings," faces the fate of its royal patrons—oblivion. It would seem that gout has almost disappeared from indexes of medical literature and been practically exiled from the reckonings of physicians. "Acute old-fashioned gout" has recently been commented on editorially as "an almost extinct disease." [396] For the last 15 years there have appeared in all jour-

nals printed in English a yearly average of only two articles thereon (Hench and Darnall [397]). Gout has by no means disappeared, as the statistics of several critical observers reveal. By them it is seen with increasing frequency; its proportionate incidence has been noted. Nor has present-day gout "gone modern" or changed its character in any important particular. The gout of today presents the same clinical pattern, the same diagnostic criteria, the same characteristic "chain of fits" as in Sydenham's day. It is, however, still very likely to be mistakenly diagnosed as either acute rheumatic fever or chronic infectious arthritis.

Definition and Pathogenesis of Gout. More than 40 years ago Osler, in his first edition (1892), defined gout as "a nutritional disorder associated with an excess formation of uric acid. . . ." Three current definitions are that gout is (1) "A disease characterized by abnormal metabolism of purines, whereby the uric content of the tissue fluids is eventually elevated, and at variable stages, usually late, salts of uric acid are deposited as tophi in particularly affected parts of the body" (Wilder [398]); (2) "A disturbance of purine metabolism characterized by an inflammation of joints, either acute or chronic, and attended in most cases by the deposition of sodium urates in or about the affected joints" (Pratt [399]); and (3) "A hereditary disease characterized by dysfunction of nuclear metabolism with an increased uric acid content in the body tissues" (Watson [400]). The chief progress discernible in these changing definitions is that Osler's idea of an excess formation of uric acid in gout has generally been discarded.

The theory of excessive production of uric acid is untenable because an accumulation of uric acid has never been found to be associated with an increased excretion or accumulation of phosphates, such as would be demanded by an accelerated destruction of nuclear protein (Wilder). However, the possibility that there may exist some source of uric acid other than nucleoprotein has not been excluded. Uric acid in birds and reptiles is mainly derived by synthesis in the liver of urea and lactic acid. Were some such synthesis possible in man, urates would accumulate without accompanying phosphates. Wilder admits that such a synthesis in man is probably incapable of demonstration, but suggests the conception that certain persons with gout may possess some such primordial metabolism as a vestigial characteristic.

Although the evidence indicating abnormal purine metabolism is associated with the most prominent features of gout, the present view is that such an abnormality may be the result rather than the cause of gout, and will prove to be a matter of secondary importance. Knaggs [197] has suggested that urate deposition is relatively unimportant in the pathogenesis of gouty arthritis, that it is the minor effect of certain metabolic changes which, in addition to urates, produce simultaneously other bodies having toxic effects. According to Knaggs, gout is closely akin to rheumatoid affections. In the absence of deposits of urates it is impossible to distinguish the gouty joint from one that has the characteristics either of atrophic arthritis or of hyper-

trophic arthritis. Numerous joints with urate deposits show other arthritic changes which completely overshadow the ones that justify their inclusion in the gouty category. Arthritic changes in the gouty joint may be caused by: (1) toxins resulting from a disordered purine metabolism, and (2) probably the equally or more important toxins that may be the same as those responsible for atrophic and hypertrophic arthritis. In the Strangeways collection nearly every specimen of gout presents hypertrophic bony phenomena which are apparently later followed by degenerative changes similar to those seen in atrophic arthritis. Inflammation set up by urates is responsible for introducing an element of confusion and intensifying the pathologic reaction. The characteristic pathologic changes in gout are illustrated in Knaggs' article by several excellent photomicrographs by Rodman. Watson has accepted the idea of Llewellyn (1927), Gudzent [401] and others, that the exciting cause of gout is cellular sensitization, in other words, an allergic response, exciting factors being endogenous or exogenous proteins of pathologic or biochemical origin, and the predisposing factor being "heredity." Alter [402] believes that gouty arthritis is at present the only definitely recognizable form of "metabolic arthritis."

Diagnosis of Gout. The usual but not always correct conception of gout is revealed in Alter's [402] description of its characteristics. "Acute gout comes on suddenly with severe pain, usually in the great toe, and most often in the middle of the night. . . . In chronic gout recognition of tophi makes the diagnosis certain. . . . The blood in a gouty subject shows a constantly higher level of blood uric acid. The roentgen-ray appearance shows the so-called punched-out areas which are deposits of urate crystals." These remarks are only relatively true, for as Hench and Darnall,[397], Wilder [398] and Watson [400] have all stated, a joint other than a great toe may be affected first, great toes may long escape involvement, and the diagnostic value of the determination of uric acid in the blood has often been disappointing, as normal concentrations of uric acid may be found in early, even in late, cases of proved gout. Tophi often do not appear until years after the initial attack; punched-out areas in bone appear also in atrophic arthritis and, when they appear in gout, they often do so too late to be very helpful.

An insistence on the "classical picture" ("toe and tophus") before a diagnosis of gout is made, is responsible for its nonrecognition in many provable (tophaceous) cases, and in many other cases of definite but early (pre-tophaceous) gout. Citing Hench's experience, Wilder emphasizes that the diagnosis of gout must depend to a large extent on a history of previous acute and generally short attacks of arthritis with complete remissions in early attacks. According to Hench and Darnall, an attack of acute arthritis in one or more joints, coming a few days after a gastronomic celebration or shortly after an operation, should be looked on as possibly gouty in nature. Patients have presented themselves in attacks of undoubted gout precipitated by the Feast of the Passover. Although surgery has been noted occasionally as one of the determinants of gout, surgical operations have not yet received

sufficient recognition as excitants of the disease. The experience of Hench and Darnall has led to the useful axiomatic generalization to " suspect gout in cases of acute postoperative arthritis." Since the advent of liver therapy for pernicious anemia, the occasional occurrence of gout during such treatment has been reported. Sears [403] reports another such instance, acute gout appearing on the thirty-sixth day of liver administration.

By those of widest experience, " irregular gout " has become a subject approached gingerly and considered with little sympathy. Schmidt [404] has reported the case of a patient with supposed gout who experienced a number of " abortive attacks " characterized by redness and swelling of the skin of an extremity without any joint symptoms. " The attack of gout ran its course, as it were, externally in the skin." (The chemistry of the blood and urine before and during an " attack " was apparently characteristic of gout. However, no tophi were present, and the fall of blood uric acid from a single value of 9.6 mg. before an attack to 1.9 mg. is a drop of unusual magnitude, of such a degree as to be viewed skeptically.—Ed.)

Roentgenograms. Roentgenographic findings in various stages of gouty arthritis have again been briefly summarized by Scott.[324] Characteristic alterations are best seen in roentgenograms of hands (or feet.—Ed.). When gout attacks a major joint, there are no roentgenographic changes of diagnostic value. Coincident roentgenograms of a hand (or foot) may be valuable, for small urate deposits are detected therein in nearly all cases of gout. Various stages of the disease, as illustrated in roentgenograms of the extremities, are, according to Scott, as follows: Very early cases show no articular changes; other changes are a single punched-out area at the base or head of bones making up a minor joint, occasionally a group of small transparent spots, frequently in the base of the first metacarpal, or involvement of the bones and joints of wrists producing characteristic carpal " mottling." Later, disorganization of joints occurs, with a loss of cartilage in joints showing gouty deposits. Irregularity and erosion of articular bone follows, and, finally, subluxation with almost complete destruction of articular bone. (In the experience of the editors, the earliest and most characteristic changes are seen in the feet more often than in the hands.—Ed.)

Treatment of Gout. While the treatment of gout is in general symptomatically satisfactory, it is not specific in any regard. The classic treatment of gout by restriction of purine, hot or cold applications, rest, and by preparations of colchicum and cinchophen, continues unchallenged. It has remained practically unchanged for years. When one recalls that aside from the use of cinchophen, introduced in 1908, there has been no major change in the treatment of gout since the introduction of colchicum in the sixteenth century, the appellation " Gout: the reproach of medicine " seems appropriate.[405] Modern investigations have in part explained the rationale but have not materially altered the ancient principles of diet in gout. Favoring the allergic theory, Gudzent and Watson search for some type of food to which their patients with gout may be particularly sensitive. One such pa-

tient was thought to be sensitive to milk and fish. "Avoidance of these quickly rid him of gouty symptoms and imparted a general feeling of well-being." Cuti-reaction tests are advised by Watson with appropriate desensitization by means of "specific antigens." "Should a gouty patient react positively to most of the cuti-reaction tests, a graduated course of peptone (Witte), 7.5 per cent, continued for two months or more will often desensitize the patient and incidentally (*sic*) relieve the gouty condition. Instead of peptone, a mixed gonococcus vaccine frequently gives remarkably good results both in gouty conditions and true rheumatoid arthritis." (The theory of specific sensitization and desensitization seems out of place if gonococcal vaccine relieves or prevents gout.—Ed.)

Cinchophen. The injudicious use of cinchophen over long periods may occasionally be responsible for a hepatitis, which may be fatal (Beaver [406]), or from which the patient may recover (Weir [407] and Comfort [408]). Many advise against the use of cinchophen, even in gout, on the ground that it is too risky. Watson feels that "iodine in the form of potassium iodide, controls the gouty state quite as efficiently and much more safely." Considering the arguments for and against cinchophen, Hench [409] concluded that if other analgesics are effective, cinchophen products should be avoided. When the former are ineffective, use of the latter is indicated. Statistical data would lead to the conclusion that the chances of a fatal poisoning by cinchophen in a given case are in reality very slight. (It has been estimated by the research department of one reputable manufacturing concern as about 1 in 600,000.) Inasmuch as we use other therapeutic agents, which have at times toxic and even fatal effects, the use of cinchophen may be justified in spite of its occasional toxicity, particularly in frequently recurring and otherwise uncontrolled gout. However, the physician and the relatives of the victim of severe hepatitis will find little consolation in statistics on the relative infrequency of such intoxications. The present yearly rate of about six reported deaths throughout the world will doubtless increase as the condition receives wider recognition. Cinchophen is sold in so many preparations and under so many names that it is almost impossible for patients taking medicine for chronic pain, rheumatic or otherwise, to avoid it at one time or another. It would seem well to keep in mind the names of the more widely advertised preparations containing cinchophen. Hench lists 30 such, with the fatalities or toxic reactions ascribed to each. (Synthalin was included in error.—Ed.)

Wilder recommends the use of neocinchophen or, if cinchophen is used, he favors Weintraud's advice regarding the use of alkalies to prevent possible depositions of urates in acid urine. When evidence of intolerance to cinchophen appears in the form of hives, skin rashes, gastric upsets, or icterus, the use of the drug should be permanently discontinued. Mothersole [410] has objected to current methods of treatment and has championed the views of Haig, "whose opinions it has long been the fashion to belittle. Those who follow Haig's teachings need not run the risk of poisoning their

patients with colchicum or atophan." Points of importance are not so much the avoidance of purines and proteins, but their ingestion in proper proportions, and particular care in the use of foods, drinks, and drugs which, according to Mothersole, interfere with the normal regulation of the hydrogen-ion concentration of blood and tissues. Various forms of physical therapy are distinctly helpful in gout. Calthrop [411] favors moist compresses, paraffin packs, and other procedures rather than local radiant heat which may be irritating and which, if used, should be applied only long enough to cause a mild hyperemia.

Comparative Value of Salicylates and Cinchophen in Gout. Sodium salicylate is known to increase the concentration of urinary urates, and many believe that it does so as effectively and in the same manner as cinchophen—through its action in the kidney whereby renal permeability for urates is augmented. Others believe that the increased concentration of urates in urine reflects an augmented excretion, due in part to an increased uric acid production or to a diminished destruction resulting from the inhibition of the uricolytic ferments. Conflicting data on the effectiveness and manner of action of salicylates in augmenting urate excretion have been reviewed previously (Hanzlik, 1927).

To avoid toxicity caused by cinchophen there has been an increasing tendency to use salicylates as a substitute. According to Denis (1915), 45 grains of salicylates have very little effect, and to produce significant increase in urinary urates it takes about 100 grains—an amount generally not well tolerated by patients, at least not for more than a very few days (Chase, Myers, and Killian (1921), G. Graham (1920 and 1926)). It has been noted also that although salicylates increase the concentration of urinary uric acid as much or even more than cinchophen, instead of preventing attacks they often provoke them (Noorden (1906) and Lublin (1930)).

According to Schroeder,[412] sodium salicylate augments urate excretion in rabbits and dogs, but only when it is given intravenously, and then only slightly. He accepts the evidence that, in man, it produces an augmented excretion. However, in rabbits and rats it also produces an increase in allantoin. From this and other evidence he believes that salicylates augment nuclear metabolism somewhat, thereby increasing the formation of the uric acid, which is followed by the appearance of more urates in urine. Salicylates may perhaps also reduce uricolytic enzyme action. Although an augmented urinary excretion of urates follows the use of salicylates, this increase does not compensate for the increase in urate production or for the possible decrease in its destruction. Schroeder found that only cinchophen and neocinchophen have a marked influence in preventing uric acid deposition or retention in the kidneys of dogs, cats, rats, or rabbits. Sodium bicarbonate and sodium salicylate have a slight effect, the bicarbonate more than the salicylate. Hexamethylenetetramine and piperazine had no effect in normal rabbits and dogs.

The Uric Acid Problem; Methods. Because the determination of blood

uric acid is such an important aid in the diagnosis of gout, the method used must be highly reliable and must not give abnormal values that cannot be explained by the clinical presence of gout or some other disease occasionally associated with hyperuricemia. Jordan and Gaston [413] found consistently high values for blood uric acid with Koch's modification of Folin and Benedict methods, using the Folin-Wu filtrate. The new method of Folin, using unlaked blood filtrate, gave considerably lower values generally in keeping with the diseases studied. They considered four mg. the usual upper limit of normal. (Osterberg [414] also believes that the Koch modification gives results which are too high. In a series of 35 cases he further determined the blood uric acid values by the Folin method on "laked blood" and by the newer Folin method on unlaked blood. The older method gave consistently higher results, the difference averaging 0.5 to 1.5 mg. per 100 c.c. of blood. —Ed.)

Physiology. Three factors must be considered in studying the concentration of urates in the human body: the amount of uric acid formed from food (exogenous) and in the process of human catabolism (endogenous), that destroyed in the body, possibly by the liver and intestines, and the amount that remains and is excreted by the kidneys. When the level of uric acid rises in blood it does not necessarily mean that more urates are being retained and less excreted; it may represent an increased urate formation or decreased destruction. When the former occurs there should be appropriate increase in urinary phosphates as well as urates. Some have suggested that a sudden rise of the blood uric acid may represent "tissue liberation"—urates suddenly liberated from tissue depots—and that the excess of urates does not represent retention, as is the general implication, but that the urates are on the way out of the body, traveling from tissues into blood and not vice versa. Thus the probable direction of a hyperuricemic flow must be considered. When the level of blood uric acid falls, it may not signify an increased excretion but a decreased formation or increased destruction. Studies on physiology concerning urates and on the pharmacologic action of various substances and medicines presumably affecting the urates must take these points into account. Thus studies on "the uric acid problem" are difficult, as one must determine not only the concentration of blood but also that of urine, and when possible, of tissues. In addition, correlated studies on sulphates, phosphates, and, in animals, on allantoin are necessary to approach an adequate explanation of the processes under observation. The problem is made more difficult because the physiology of animals is not the same as that of man, and that of the patient with gout is again obviously, at least in some regards, quite different from that of the normal man or normal animal.

Studies on metabolism of uric acid in various animals do not reveal information directly applicable to human physiology, as metabolism of uric acid is not similar in different vertebrates. However, they do yield important data. Birds and reptiles excrete large amounts of uric acid in the

urine; as before stated, uric acid in them is formed mainly by synthesis of urea and lactic acid in the liver, a minor part arising from nuclear metabolism independent of the liver. Most mammals do not form uric acid from urea but only from products of nuclear metabolism. By a series of enzymatic reactions, uric acid is formed from nuclear protein, and almost all of it is excreted as such. In dogs (except the Dalmatian), uric acid is excreted normally only in traces, as it is almost entirely oxidized by liver enzymes and excreted as allantoin. Removing the liver, Bollman and Mann [415, 416] show that this destruction or conversion of uric acid is completely prevented, urinary allantoin progressively decreasing and large amounts of uric acid appearing in blood to be excreted as such in urine. Injection of uric acid into a liverless animal was followed by its almost quantitative recovery in urine unchanged. Bollman and Mann conclude, therefore, that in dogs, the formation of uric acid is independent of the liver, but the destruction of uric acid (and formation of allantoin) depends entirely on the liver.

It is believed that in man uric acid is eliminated by glomeruli and reabsorbed by cells in the loops of Henle. Renal tissue has a peculiar affinity for urates. It retains injected urates in large amounts, and in animals at least, these urates which are stored in the kidney are not promptly excreted in urine but are first returned to the blood (Folin, 1924). It is believed by some that gout represents a state of abnormal renal tropism or affinity for urates resulting in a diminution of excretion. Medicines that are effective in gout are thought to act by altering this affinity of kidneys for urates, or by increasing urate excretion, possibly by diminishing the extent that it is reabsorbed in the loops of Henle.

In man, the fate of injected urates is not clearly understood. Large, amounts are unrecovered, and apparently destroyed. In dogs, since most of the uric acid of either endogenous or exogenous origin is oxidized to allantoin, Wilhelmj and Moskowitz [417] have proposed the study of uric acid tolerance curves, the rate of disappearance of injected urates being an index of urate destruction. Following a single intravenous injection of uric acid, the blood uric acid rose to a high level and then began to drop. By replotting the curves, with the logarithm of the blood uric acid concentration against the time after injection, they found that the rate of disappearance was about 3 per cent per minute and that it followed a logarithmic curve suggesting a monomolecular reaction in which one molecule of uric acid is oxidized to one molecule of allantoin. The uric acid excreted in urine was small in amount, varying between 2.7 and 5.5 per cent of that injected. The continued injection of uric acid revealed that the ability of dogs to destroy uric acid is sharply limited. The effect of an added single injection during a continuous injection was also studied. Comparing these results with those in man, it was suggested that the difference between dog and man in this respect may be quantitative rather than qualitative.

The effect of the methylated xanthines, theophylline, theobromine, and caffeine, on the uric acid excretion of Dalmatian dogs was found by Hanzal

and Meyers [418] to be essentially the same as that for man. There was no change in the quantity of uric acid excreted after administration of theobromine, but a marked increase after theophylline and caffeine. The solubility of several methylated uric acids was found to be much higher than uric acid. Those differences were made use of in a separation of the uric acid excreted after the ingestion of the methylated xanthines. Dreyer and Young [419] studied the effect of various substances on the excretion of uric acid and urates by cockerels. They found that, of solvents for uric acid, the intravenous injection of lithium carbonate in isotonic concentrations is most effective, inducing marked diuresis and increasing the output of uric acid many fold. Lithium chloride, caffeine, theophylline, euphylline, colchicine, and epinephrine do so also; piperidine, piperazine, ethylene diamine, and hypertonic solutions of glucose, sodium sulphate, sodium chloride, and sodium bicarbonate increase the excretion less effectively. Methylamine, guanidine, and hexamethylenetetramine are ineffective. Theobromine and the salicylates are entirely negative.

Hemophilic Arthritis: "Bleeder's Joints." The development of newer ideas on hemophilia has resulted in the appearance of several interesting reports on hemophilic arthritis (Rutherford,[420] Freeman [421]). Key [422] has given for the first time in English a detailed report on its pathology, and Keefer and Myers [83] describe clinical and roentgenologic features in five cases, with a review of the literature. According to Howell's theory, hemophilia is the result of a disturbance of blood platelets, which may be normal in number and morphologic appearance, but which fail to yield cephalin necessary for normal clotting processes. Konig (cited by Key) previously recognized three states of hemophilic arthritis: (1) simple acute hemarthrosis, with single repeated hemorrhages into joints, with pain and limitation of motion, (2) panarthritis, the form associated with an inflammatory process in joints, fever, hemarthrosis, and exudation into the joint, changes in synovial membrane, capsular thickening, with organization or exudate resulting in fibrosis, limitation of motion, swelling, and discoloration of joint surface, and (3) the chronic inflammatory stage, with chronic changes in joints and destruction of articular cartilages as in arthritis deformans. Key cannot differentiate the second and third types, and recognizes only two stages, that of acute hemarthrosis, and the stage of chronic arthritis.

Acute hemarthrosis usually follows some sort of an injury, but may occur spontaneously even while the patient sleeps. Pain and swelling may be slight or intense, varying with the degree of intra-articular pressure. Local heat and redness are generally not present, but periarticular tissues may appear cyanotic. Extrasynovial hemorrhages may appear as discolorations. There may be slight fever and moderate leukocytosis. In roentgenograms, bones may be normal in the acute stage but the joint is distended with blood, which casts a shadow denser than in ordinary acute synovitis. An irritative

hyperplasia of synovial membrane results from hemorrhage and pressure therefrom. Subsynovial tissues become thickened by fibrous tissue and contain large amounts of iron, in turn containing blood pigments which, according to Keefer and Myers, often cast a dense roentgenographic shadow and may be incorrectly interpreted as calcification. Macrophage cells accumulate in subsynovial tissue and migrate back and forth between the joint cavity and synovia, phagocytosing the erythrocytes, the pigment of which remains in the macrophage cells. When the blood is absorbed the tissues tend to return to normal. Each new hemorrhage adds irritation, and synovial villi form. After many hemorrhages, joints may fail to return to normal. Stiffness, swelling, and pain may ensue for weeks or months, progressing by remissions to the stage of chronic arthritis. Fibrous ankylosis may occur; bony union rarely results. The cartilage eventually erodes, at its margin, by encroachment of the hyperplastic synovial membrane, such as occurs in atrophic arthritis. A spotty destruction of articular cartilage occurs, the areas of destruction being irregular in contour, a characteristic of hemophilic arthritis. Cavity or cyst formation may result from subperiosteal hemorrhages or those in subchondral bone. Roentgenograms in the chronic stage present a variable picture, suggestive at times of tuberculosis, of chronic atrophic or hypertrophic arthritis, even of osteochondritis, and Key, Keefer, and Myers agree that they are not pathognomonic. The diagnosis of hemophilic arthritis rests chiefly on the history of a bleeding tendency and the onset of acute joint swelling after minor injury. The coagulation time is usually increased but may be normal. Aspiration of a joint for blood may at times be risked, using a very small bore needle.

Treatment of Hemophilic Arthritis. Birch [423] has attempted to confirm Howell's theory and to show that, in men, hemophilia is apparently the result of a lack of ovarian hormone. As a result of her work, the idea of ovarian therapy, first suggested by Grant (1904) and Wright (1909) has been revived. White [424] prevented further hemarthrosis, in a boy, by repeatedly giving 0.5 c.c. of theelin, intramuscularly. When ovarian extract failed to control hemorrhages in two cases, Bernstein [425] gave 10 to 15 c.c. of whole blood, intramuscularly, every other day, taking the blood from the patient's mother, during her menstrual cycle, and continuing for a few days thereafter. (According to Matagne, 1932, Chalier considers frequent injections of mother's serum the most efficient treatment of all.—Ed.) Kimm and Van Allen [426] injected 4 grains (0.26 gm.) of ovarian extract "azoule," an English preparation, to prevent further bleeding in a boy with hemophilic Volkmann's contractures. Spoto [427] considers the use of ovarian extract (Lilly No. 177) by hypodermic, and later by mouth, successful, but Freeman [421] cited failures, and progynon failed to hasten clotting time in a case of Brown and Albright's.[428] Key has outlined additional treatment for the joints: in the acute stage, complete rest and immobilization in plaster or splint; in the chronic stage, correction of deformities by traction or wedging plasters, and if necessary, supports such as roller bandages and occasionally

a walking caliper. Under no circumstances should the joint be manipulated or opened (Keefer and Myers [429]).

Joint Conditions Associated with Purpura. Schönlein's purpura (peliosis rheumatica) and Henoch's purpura (purpura nervosa) are associated with joint pains and swelling, and are classified by Otto [430] under the anaphylactoid variety of the primary type of non-thrombocytopenic purpura. In the former type epinephrine is used. The latter type, Henoch's, is thought to be due to the histamine-like action of split protein products absorbed into the body.

Miscellaneous Types of Joint Disease

Intermittent Hydro-Arthrosis. This is a rather rare disease, only 77 cases having been reported up to 1921 (Bierring). Affecting the sexes equally, it involves the knees most commonly. It is not possible to place it accurately in an etiologic classification as its cause is unknown. It is variously considered as a vasomotor neurosis related to angioneurotic edema, an endocrine disturbance, or an allergic reaction to bacteria or other agents. Distinction should be made between two so-called types, idiopathic and symptomatic. The first is presumably a painless intermittent "synovitis," or synovial effusion, occurring more frequently among young adult women. Some believe it to be related to menstrual irregularities. This type represents the rare true form of intermittent hydrops which, were it essentially a functional affair, would be expected to recur and remit more or less indefinitely yet produce little or no organic residue. Intervals of freedom generally vary from 7 to 21 days, usually being 11 to 12 days. The second or symptomatic type seems to be associated with arthritis and is less rare. Representing probably the early stage, it is perhaps the synovial element of a very slowly progressive arthritis, with complete remissions in symptoms but probably not in pathologic changes. Because of its rarity, a study of the pathologic findings in one case (apparently of the second type) by Porter and Lonergan [431] is of special interest. When it was unrelieved by the usual treatments (desensitization with peptone injections, intravenous TAB vaccine, arsenic, quinine and its derivatives), synovectomy was performed on both knees. Pathologic changes in synovia resembled those found in atrophic arthritis: villous formation, thickening of synovial membrane, and mononuclear infiltration. The subsynovial layer, however, was markedly edematous; in some such areas the edema was replaced by fibrinous hyalinization, which with edema would be unusual in ordinary atrophic arthritis. Hydrops had recurred, with little variation, 9 years prior to operation, but had not returned five years after synovectomy. However, a progressive arthritis of hips and spine appeared.

Synovectomy was performed in two cases reported by Krida.[432] The swelling in the first case initially followed trauma; thus it may represent the symptomatic type. Skin tests to 137 substances, foods, and organisms were

negative. Operation was done during the period of hydrops. Blood counts and studies of the synovial fluid were normal. Sections of synovial membrane showed flattened villi, new granulation tissue, edema, and profuse round cell infiltration. The second case was related to menstruation and was apparently of the idiopathic type. Synovectomy was done during the quiescent period, hence differences in pathologic findings were noted: long slender villi, well formed connective tissue, only slight edema, and moderate round-cell infiltration. Effusions had not recurred within one year and within eight months after operation, respectively.

Krida has reviewed factors of age, sex, race, heredity, and the possible etiologic connection with trauma, infection, arthritis, menstruation, pregnancy, psychic disturbances, and sensitization. Under ordinary circumstances the prognosis for therapeutic or spontaneous cessation is not good, though both occur. Good results were obtained from synovectomy by Bernstein in " several cases " of " recurrent hydrops."

" Mixed Types " of Joint Disease. Certain patients present mixed types of arthritis and search may show an obvious combination of at least two causative influences or of two clinical types. Coates [433] describes combinations under the following headings: atrophic arthritis and gout, atrophic arthritis and arthritis of the menopause, atrophic arthritis superimposed on hypertrophic arthritis, and gout and hypertrophic arthritis. (Although patients with atrophic arthritis in later life often get hypertrophic arthritis, is not this to be expected, since the latter is almost universal after the age of 50? Cases illustrating the unmistakable combination of atrophic arthritis and gout are rare. Coates' cases do not clarify the issue. They seem poorly chosen to prove the point and clinical data are scant. Thus of four patients with supposed gout only one had tophi and two without tophi were women. Provable gout in women is very rare, and the statement that the " uric acid was high " and roentgenographic " cysts " were visible is not enough, without considerable more data, to convince critical readers that gout was present or that a mixed arthritis was in fact observed.—Ed.)

Arthropathia Psoriatica. Psoriatic arthritis has been neglected in the English and American literature. Psoriasis and arthritis may occur together casually and quite independently, but often in cases of long standing psoriasis a characteristic involvement of joints may occur which is favorably influenced by treatment of the skin condition (Garrod and Evans, 1924). Two cases of pustular psoriasis with arthritis are reported by Hunt.[434] Pain and stiffness in joints varied with the skin condition.

Of 53 patients with psoriasis studied by Hunt,[435] 70 per cent were suffering with " arthritis or rheumatism," 80 per cent had relatives with some form of rheumatic infection, and 35 per cent gave a familial history of psoriasis. Because her patients complained of no one type of rheumatism but had, variously, atrophic or hypertrophic arthritis, rheumatic fever, or fibrositis, she does not recognize a specific type of psoriatic arthritis. Because the histology of psoriasis has several points in common with that of

clinical or experimental rheumatic nodules, she suspects that the two diseases have a common cause, probably streptococcal. (It is likely that Hunt saw cases of true psoriatic arthritis but did not recognize the entity and confused it with other types of rheumatism incidentally associated with psoriasis.—Ed.) Without mentioning arthritis Jamieson [436] has reviewed the various theories on causation and treatment of psoriasis, outlined his favorite diet therefor, and considered the possible relationship of the disease to some endocrine abnormality, possibly of the pituitary gland.

Arthritis and Leukemia. A related arthritis is exceedingly rare in cases of leukemia although bone pains occur. Four cases of arthritis associated with leukemia are reviewed by Smith.[437] Two new cases are reported: one by Poynton and Lightwood [438] and one by Smith; in both cases the preliminary diagnosis was acute rheumatic fever. In the first, a girl, three years old, had fever and migratory joint pains, and later cough and a swollen tender ankle. The liver and spleen were barely palpable. The blood picture was that of an aleukemic phase of acute lymphatic leukemia (erythrocytes 1,125,000, leukocytes 4,700 per cubic millimeter, and lymphocytes 82 per cent). At necropsy, leukemic periosteal and medullary infiltrations were found. Various cultures were negative. In Smith's case a boy, three years old, was observed over a period of nine months in four acute exacerbations of acute polyarthritis that resembled rheumatic fever but were resistant to salicylates and other treatment. Lymph nodes, liver, and spleen were enlarged. The erythrocytes fell to 1,000,000 per cubic millimeter, the hemoglobin to 15 per cent. The leukocyte count varied between 18,000 and 680 per cubic millimeter. The diagnosis was leukopenic myeloid leukemia. Roentgenograms revealed periosteal thickening, cortical erosion, and medullary rarefaction. Death occurred in one year.

"Hysterical Joints." The diagnosis and treatment of this condition are given by Ogilvie.[439] A dancer, 18 years old, fell and thereafter complained of pain in the hips and knees for which no relief was obtained by various treatments, including removal of the external cartilage from both knees. Muscle spasm, great pain, and limitation of motion in hips and knees were present, but no atrophy of muscle, shortening, swelling, or abnormal reflexes were found. (Roentgenograms were not mentioned.) Significant pain in joints is almost invariably accompanied by wasting of related muscles. "If there is no wasting the pain is either slight or imaginary." According to Ogilvie, disease of both hips and knees without involvement of upper extremities is almost unknown, occurring neither in tuberculosis nor in gonorrheal or atrophic arthritis. Psychotherapy was successful.

Periarthritis of the Shoulder. Such a term seems preferable to Dickson,[440, 441] and Dickson and Crosby [442] to "painful shoulder," "subdeltoid bursitis," or "subacromial bursitis," for the entity which it signifies results from a complex pathologic state in which not just a bursa is involved but also capsule, ligaments, and tendons at the shoulder. Characteristics of the syndrome are: the onset of pain, with or without trauma; the pain is

aching, or sharp and stabbing, sometimes severe enough to require morphine. Pain is felt a few inches above the insertion of the deltoid and may continue as a neuralgia down the arm. Sensation and reflexes are normal. The characteristic limitations are pain beyond abduction of about 45° and on attempting full external or internal rotation. Forward and backward motions are not limited and are painless. Sometimes abduction is only painful between 70 and 90°; beyond that angle it may be painless. Atrophy of muscle may appear. Calcification may be present in the supraspinatus muscle.

From a study of 200 cases Dickson and Crosby concluded that some general physiologic disturbance was responsible and that an exact evaluation of the importance of any one factor (trauma, infection, metabolic derangement) was impossible. Regardless of probable cause and whether treatment was removal of foci, physiotherapy, manipulation, or surgery, the time required for duration of the disease was remarkably constant, from one to six months. Cases were equally divided between the sexes; in most the condition occurred after 40 years of age and oftener in the right shoulder. In 13 cases both shoulders were involved. Trauma was reported in 34 per cent of cases, infected foci in 88 per cent, and metabolic disturbances (diabetes, hyperthyroidism or hypothyroidism) in 16 per cent. Thus in the majority of cases more than one possible cause was noted. Calcification was seen in 37 per cent and did not bear any relation to the severity, duration, or possible cause of the condition. It is no invitation to operation and tends to disappear under conservative treatment. Removal of the calcified area in five cases did not hasten recovery.

Treatment consisted of removal of infected foci, regulation of metabolism, a high vitamin-low carbohydrate diet, heliotherapy, and, in the acute stage, immobilization of the arm in moderate abduction and external rotation by means of traction. On the third day, diathermy and passive motion were instituted. Ninety-four per cent of patients recovered completely in one to six months. In 13 cases polyarthritis developed elsewhere in the body.

In many cases of bursitis at the shoulder, pain is relieved by downward traction of the arm, according to Ferguson [443] who has devised a simple apparatus therefor. Radiotherapy relieved Kahlmeter's [22] patients. "Cross-fire diathermy" and gentle exercises are approved by Kovacs [444] for subdeltoid bursitis; he places reliance on Dawbarn's sign (when the arm hangs by the side, palpation over the bursa causes pain which disappears when the arm is abducted). The sign is valueless according to Hitzrot,[445] who favors rest, sedatives, and hot moist applications in the acute stage rather than dry heat, diathermy, and massage. As the acute condition subsides, gradual abduction is indicated. Operation is generally only indicated in acute traumatic bursitis to remove blood and exudate from the bursa and to repair tears of the supraspinatus tendon. Cave,[446] Beer,[447] and Gordon [448] all felt that deposits of calcium were no indication for operation, that they frequently resorb, and that while it is easy to operate it is not easy to find

the calcification. If anything goes wrong, the surgeon leaves as much damaged tissue as he approaches. Surgical removal of calcified deposits is only indicated, Hitzrot feels, when they do not disappear and are associated with recurring attacks and residual disability. (Aspiration or surgical rupture of certain bursae is at times as beneficial as resection.—Ed.)

Diseases of Muscles and Fibrous Tissue

Muscular Rheumatism, Myositis, and Fibrositis. Ignorance and confusion attend clinical and etiologic segregations of diseases of muscles even more than of joints. They are considered under two groups: the commoner ones, myalgia, "growing pains," fibrositis or myofibrositis, and infectious myositis, and the less common ones—myositis ossificans progressiva, progressive myositis fibrosa, and dermatomyositis.

Myalgia and "Growing Pains." The myth that normal physiologic growth may cause muscle pains has been exploded. Transient muscle pains of short duration are believed generally to be due to unappreciated sprains, minor injury, or passing infections. Chronic muscle pains may be due to chronic fatigue of normal muscles, fatigue of muscles affected by orthopedic abnormalities (flat feet, scoliosis), and infections or toxins. In many cases of myalgia no pathologic basis is discovered. Some suggest that the pains result from bacterial toxins, toxins of fatigue, an irritation of nerve endings, or to the actual lodgement of germs in capillaries and tissue spaces. At any rate, myalgia is but a symptom of several disease conditions, not an incident of normal growth. It may eventually be possible to classify disease of muscle etiologically: traumatic, infectious, chemical, neurogenic; to date, however, only clinical patterns can be given.

Fibrositis. It has been shown that what is generally called "muscular rheumatism" is in reality not a myositis in the sense that primary parenchymatous changes in muscle cells are visible. Indeed, true myositis, in the latter sense, is rare. Common "myositis," or "muscular rheumatism," has been more properly designated as "fibrositis" by Gowers (1904), Stockman (1904 and 1920) and others, since its pathologic characteristics are interstitial not parenchymatous, an inflammatory hyperplasia of supporting fibrous tissue. Inasmuch as the reaction may affect fibrous tissue, not only of muscles but anywhere in the body, the symptoms and anatomic types of fibrositis are varied as fibrous tissue of fascia, aponeurosis, tendons, capsule, and periosteum are involved. Thus bursitis is sometimes spoken of as bursal fibrositis, a sciatic neuralgia as fibrositis of the coat of the sciatic nerve. Fibrositis may be local (in a bursa, nerve, ganglion, one tendon attachment, or one muscle group), or generalized. Thus various writers include under fibrositis such manifestations as lumbago, wry neck, tennis elbow, tender heels, Dupuytren's contracture, diffuse muscular fibrositis or "neuromuscular pains," tendinitis, "capsular rheumatism," and also sciatic or brachial fibrositis (Willcox, Brown,[290] Buckley [449]).

The general and sex incidence of fibrositis has been noted (ANN. INT. MED., 1935, viii, 1321). It may constitute from 15 to 62 per cent of cases in various series on "rheumatism." It is more common among men than women (Coates and Delicati [23]), and among miners and outdoor workers (Buckley,[449] Holt [24]) than others. With atrophic and hypertrophic arthritis, it makes up the three great types of chronic rheumatism.

Its pathologic characteristics are reported (Stockman (1920), Brown [290]) as diffuse and localized inflammatory hyperplasia of fibrous tissue. The localized areas may be palpable as nodules, tender areas of infiltration in muscles or near tendon attachments. The nodules consist of a core of granular débris, presumably disintegrating small, round cell infiltrations, surrounded by concentric fibroblasts. By special staining Stockman showed occasional nerve fibrils embedded in nodules, hence their painful character. English writers stress particularly the diagnostic importance and apparent ease of finding nodules. Some insist on their presence for a diagnosis; others admit that in many cases of fibrositis no nodules are felt. Even when nodules are felt they may not reveal pathologic change, according to Nicola [382] who describes "myogeloses" as definite, sharply-localized areas of hardening 0.25 to 4 cm. long, in muscles, chiefly gluteal. They may be the cause of low back pain and are distinguished from the indurations of myositis in that biopsy is negative. According to him they are due to localized interference with circulation and to local increase of lactic acid.

Etiology of Fibrositis. Some consider all forms of fibrositis of infectious origin; others believe one can have traumatic and other forms of fibrositis (gouty, toxic, and so forth). The chemical and pathologic differences between localized acute fibrositis (e.g. lumbago), chronic diffuse fibrositis (diffuse muscular rheumatism), and the fibrositis which is part of rheumatic fever are not established. Brown looks on the reaction as a defensive one—an attempt to shut off the activity of the invading agent. Willcox [198] believes streptococci responsible. Seham and Hilbert [450] consider certain proposals: that the muscle pain is the result of colloidal changes, a general hyperalgesia, or of fatigue toxins accumulated as the result of circulatory disturbances and oxygen deficit in muscle. Cold and damp are predisposing factors (Buckley [449]).

The "muscular rheumatism" of children was studied by Seham and Hilbert: 21 per cent of 208 children from 8 to 15 years of age had muscle pains of from three months' to three years' duration. Statistics of others vary between 7 and 44 per cent. There were relationships between muscle pains, inadequate sleep, and fatigue. Some had had occasional fever, but no more than a normal group would have had. Of those with continuous fever 30 per cent developed systolic murmurs as compared to their appearance in only 19 per cent of those who were afebrile. Nodules were not found. The presence, absence, or removal of tonsils seemed to play no rôle. The average agglutinative titer of serums for the normal group was 1 : 160, for those with muscle pains, 1 : 1,500. It was concluded that infection was

probably the cause of such muscle pains, at least some of which were related to rheumatic fever. Pains of chronic fatigue affect chiefly muscles of the lower extremities, are not migratory, not associated with joint pains, not affected by seasons of the year, are absent during sleep, and are cured by "adequate health schedules."

Common sites for fibrositis are: muscles of the scalp and back of the neck, erector spinae, muscles of the loins and buttocks, and those of the shoulder, intercostal, or pectoral regions. Pain frequently is projected down the arms (Buckley).

Treatment of Fibrositis. The treatment of muscular fibrositis is essentially similar to that of other forms of rheumatism: rest and heat, removal of foci, proper clothing and climate, analgesics, and sometimes vaccines. Buckley approves of the use of a hot flatiron applied to the back over a layer of thick brown paper when less primitive measures are not readily available. Sunshine is more useful in fibrositis than in arthritis. Roentgenotherapy relieved 65 per cent of 34 patients with lumbago who were treated by Kahlmeter.[22]

Tendinitis. Tendinitis may appear as part of atrophic arthritis, gout, or rheumatic fever, but it is often an independent entity. Kahlmeter [451] has discussed the various forms of localized and general tendinitis. Subdeltoid or other calcareous bursitis may in fact be localized tendinitis, other examples of which may be seen at tendon insertions of the great trochanter, the inside aspect of the knee, and the calcaneal spur. "A little known but not uncommon form" is that at the insertion of the quadriceps tendon at the upper border of the patella. Roentgen therapy is his favorite treatment, heat and massage being "rarely of any use." Kahlmeter considers trauma the most likely cause of quadriceps tendinitis.

Dupuytren's Contraction. An extensive review of this disease is given by Davis and Finesilver.[452] Some consider it fibrositis of the palmar aponeurosis. It is a "focal hypertrophy of the connective tissue originating in the wall of the smallest vessels and ending in contraction." The usual etiologic factors, of heredity, trauma, infection, and endocrine deficiency, have been proposed and are discussed by these authors, who conclude from a study of 40 cases that the cause is unknown. Mild trauma may act as an inciting or contributing factor; it is not the specific cause, nor is there any known constitutional disease with which it is exclusively associated or of which it is a manifestation. The clinical course begins insidiously, with the formation of a small nodule or slight induration of the skin on the palmar surface of the hand, at the base of the fourth or fifth fingers, and slowly progresses in characteristic fashion. When the process has existed for some time, tendons become shortened and joint surfaces are changed in form on account of the change in pressure, becoming atrophic where the greatest pressure occurs. Joints may finally ankylose. It was more common among men (35 cases) than women (five cases) and among diabetics than nondiabetics (six of 200 diabetics had it). Medical measures seemed to be of

no avail once it had progressed. Excision of palmar fascia and digital fasciculi are advised. For reasons stated, the authors propose in the future to try division of the palmaris longus tendon in the wrist, in early cases.

Myositis Ossificans Progressiva. This is a rare disease of the locomotor system which occurs among children during the period of growth and affects not only muscles but tendons, ligaments, fascia, and aponeurosis. It is characterized by the appearance of areas of calcification. There is no ossification of muscle, as muscle cannot turn into bone. There is ossification of fascia, and the formation of new bone is intermuscular, not intramuscular. Thus Grieg's term, "fibrositis ossificans progressiva," is more accurate. The condition proceeds by a series of acute exacerbations and remissions. Mair [453] has reviewed the features in the 72 cases in the literature and added two cases of his own. An extensive review of ideas on cause, pathology, and treatment is included, but the former is admittedly unknown and no treatment seems helpful. It must be distinguished from myositis fibrosa, dermatomyositis, polymyositis hemorrhagica, and calcinosis interstitialis. A case of myositis ossificans is added by Jamieson.[454]

Generalized Myositis Fibrosa. This is the rarest of all generalized chronic myopathies, there being only 4 authentic typical cases reported, according to Schwab, Brindley, Bodansky, and Harris [455] who add a case of their own. Its characteristics are briefly: insidious onset of stiffness and muscular clumsiness, weakness, loss of weight, progressive muscular disability, a doughy feel to muscles at first, later a sense of board-like hardness. Pain is not a striking feature. Biopsy of muscle shows degeneration, inflammation, and fibrous tissue changes, the disease being chiefly parenchymatous. Studies on creatine metabolism showed a definite relation between the degree of inflammation and the amount of creatine which the muscle contains and which it is capable of storing. Marked creatinuria and an extremely low tolerance for exogenous creatine were features of perhaps diagnostic importance. The cause is unknown. The prognosis is poor—death usually occurs in a few years. Specific treatment is unknown.

Sciatica

Sciatica, or sciatic pain, is generally divided into two groups: (1) primary or idiopathic sciatica, in which pain is apparently the result of pathologic processes involving the nerve itself, producing "sciatic neuritis" and (2) secondary or "symptomatic sciatica," or "sciatic neuralgia," in which the pain is the result of factors which affect bones and muscles primarily and involve the nerve secondarily. Several (Gardner,[456] Williams,[457] Pringle,[458] and Craig and Ghormley [459]) have reviewed these types, and the causes and treatment of the sciatic syndrome. Gardner classifies sciatica as follows: (1) the sciatic syndrome secondary to general disease, such as syphilis, diabetes, lead poisoning, and alcoholism, to tumors, or to "true inflammations" of vertebrae, pelvic bones or pelvic organs (in such cases pain is often bilateral and wasting of muscle or paralysis and disturbances in

sphincters may be present), (2) true sciatic neuritis, a rare disease, caused by exposure and infection, (3) sciatica due to myositis or fibromyositis, and (4) sciatica due to neurodocitis—an inflammatory condition of the intervertebral bony canal through which the nerve passes. From 80 to 85 per cent of the cases belong to the last two types.

Of 85 cases of sciatic pain studied roentgenographically by Williams, 80 (94 per cent) showed pathologic changes in tissues or joints, considered to be the cause of the nerve irritation. A narrowed lumbosacral disk was found in 59 cases, hypertrophic arthritis in 15, sacro-iliac arthritis in three, spondylolisthesis in two, and lumbosacral anomaly in one.

Among patients with sciatica there is frequently a contralateral scoliosis, a spinal tilt away from the affected side. Less commonly the trunk may list to the affected side, homolateral scoliosis. Capener [460] saw three cases in which the scoliosis alternated from the contralateral to the homolateral side and back again. An instance of sciatica with paralysis following forceps delivery was encountered by Burgess [461]; recovery followed rest, splinting, and massage. By simply increasing the heel-length of the right shoe, Hench, Wakefield, and Camp [462] promptly cured a patient with persistent sciatica resistant to all usual measures, and found to be associated with, and apparently due to, postural trauma incident to congenital hemi-hypertrophy and shortening of the left leg.

Treatment of Sciatica. Ultimate success in treatment obviously depends on determining the likely one of the many causes noted. In general, rest in bed, heat, and analgesic drugs are indicated. Epidural injection is advised if these do not suffice (Gardner). Later detailed investigation must follow the acute phase. Treatment varies with the findings. Immobilization by strapping with adhesive plaster or casts may be necessary (Gardner, Williams). When significant symptoms recur, in appropriate cases Williams favors lumbosacral fusion. The results of various treatments and combinations of treatments of 159 cases of sciatic pain of indeterminate origin were analyzed by Craig and Ghormley; of these, 177 patients were ambulatory, 42 bedfast. In the former group of 80 treated with epidural injections alone, only 52 per cent were completely relieved. Obviously, other measures are indicated. Diathermy alone completely relieved 33 per cent of 36 patients; a belt and diathermy completely relieved 33 per cent of 52 patients. Injections and diathermy helped more, but the best combination was the use of epidural injections, diathermy, and a belt, by means of which 85 per cent of the group so treated were completely relieved. Of those confined to bed, 86 per cent of 28 patients were completely relieved by the use of a double Buck's extension, diathermy, epidural injections, intravenous foreign protein, and removal of foci. Of 14 patients treated similarly except that epidural injections were omitted, 63 per cent were completely relieved. Thus epidural injections gave added relief. They are also approved by Fulcher,[463] Fletcher,[256] L. F. Miller,[464] and Bankart.[377] Forty to sixty cubic centimeters of a one per cent solution of procaine hydrochloride seem favored.

Physiology of Joints. The last should be first. A full understanding of the pathogenesis and treatment of diseased joints must be based on a comprehensive knowledge of the physiology of normal joints. Information on this subject is meager, and only a few workers seem to be putting first things first, going back to essentials. Much time is spent on a search for bacteria, on analyses of blood, urine, feces, and so on, but only a few bold spirits dare to violate the integrity of the joint cavity to study the cytology and chemistry of articular tissues in health and disease. Colloids and other substances are hopefully administered by vein, without our knowing whether the particular colloid will ever arrive at joints in significant amounts. So little is known of the blood and nerve supply of joints, of the origin of synovial fluid, of its physiologic reaction to different agents. Vaubel [465] studied the growth of synovial tissues of rabbits. There developed polymorphic cells clearly different from fibroblasts. These synovial cells are peculiar in producing mucin and a proteolytic ferment, and in forming in their cytoplasm large, highly-refractive granules. They can coagulate plasma under certain conditions. A function of these cells is to produce mucin for synovial fluid. Vaubel concluded that synovial fluid is a persistently liquid, ground substance derived from these special synovial cells which he calls "synovioblasts." Speculating on the etiology of atrophic arthritis, Bauer, Bennett and Short [220] ask whether it is possible to produce the proliferative changes of this disease by simply interfering with or altering the physiology of a normal joint. From experiments they conclude that synovial fluid is probably a simple diffusate from rich subsynovial blood vessels, that proteins can be removed from joints only by way of lymphatics, and that albumin can leave joints with comparative ease, globulin with great difficulty. The size of a molecule that can be removed from a joint with ease lies, therefore, somewhere between a molecular weight of 72,000 and 175,000. If proteins are not removed from joints as rapidly as they gain entrance, an effusion results and is maintained. Thus a joint effusion may result from too rapid diffusion of plasma filtrate from subsynovial blood vessels into the joint cavity, from interference with the removal of proteins, or from a combination of these two factors. An increased permeability of vessels from any cause may result in a more rapid formation of synovial fluid, much richer in protein than normal. This increased protein attracts more water because its presence greatly increases osmotic pressure. Given a joint effusion, we have an ideal culture medium for connective tissue growth because it has a high protein content and contains fibrin and constituents of serum. The continued presence of fibrin is probably followed here, as elsewhere, by proliferation of fibroblasts, and vascular endothelium.

The importance of studies of this fundamental type is being increasingly recognized. Far-seeing clinicians are urging more studies of the patient's soil, less perhaps of the seeds of disease, for if the soil is not receptive the seeds fall by the wayside, harmless saprophytes. The determination of what agents *can* produce disease in joints may help to show what *does* produce a

given type in man, but while studies continue on likely agents, inquiry should be pressed regarding the sociology and chemistry of those recognized as physiologic candidates for the disease as well as of established hosts. Major secrets concerning arthritis await him who will but study the soil, especially the chemistry, of articular tissues in health and disease.

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EDITORIAL

ON WORMS

THE influence of intestinal parasites upon the health of the host has been a matter of lively discussion both in medical and lay circles through the ages. There have been periods when it was customary to attribute almost every possible malady to some harmless or even to some totally imaginary helminth parasite. Contrariwise in some ages medical opinion has favored the view that such parasites were not only harmless but indeed helpful, stimulating the digestion as some thought by consuming the excess of chyme. Even today there are native peoples such as the Abyssinians who are dissatisfied with the condition of their health if their stools do not contain segments of taenia. Those who are presumably better informed will perhaps question this criterion of well being; a wider knowledge of the variety of worms in the animal kingdom will enable them to discuss these under the headings of the platyhelminthes or flat worms and the nemathelminthes or round worms and to point out that either in the larval or adult stage one or another of these helminths may parasitize nearly every organ and tissue in the human body. Even in the cases of those worms which in the parasitic stage remain confined to the intestinal tracts of their hosts there are some concerning whose pathogenicity very little doubt exists. The very name given to our common hookworm *Necator americanus* (American murderer) is an indictment; and the relationship of *Diphyllobothrium latum* to a severe macrocytic anemia is widely accepted. If, however, someone with a leaning towards the Abyssinian point of view were to question one of the well informed still more closely, especially as to the nature of this pathogenic action of the intestinal helminths, it would not be difficult to disclose a quite surprising state of ignorance.

Surprising, because after all physicians have been acquainted with worms in the intestine since long before Hippocrates. The Egyptians fifteen hundred years ago knew ascaris and oxyuris and taenia. Hippocrates himself held to a theory that worms were formed in the fetus and hence were present at birth. Later the mode of origin of worms became the test case in the endless discussions of the theory of spontaneous generation. Redi, the father of parasitology, in 1684 put a temporary quietus upon the uproar by describing the male and female forms of certain intestinal worms, the existence of ova and in particular by picturing the reproductive organs of *Ascaris lumbricoides*. Truth was not long triumphant in this instance and spontaneous generation remained a live topic until the time of Pasteur. Shortly after Redi, a member of the Faculty of Paris, Nicolas Andry, took up in quite serious fashion the possible relationship of worms to human pathology. So virulently was he criticized by his colleagues that he humbly withdrew his assertions; and those who had followed his lead in other medi-

cal centers of the day were likewise silenced by ridicule. Guiart makes the diverting statement that this historic controversy begun in 1700 still persists in the Faculty of Paris, where, apart from the parasitologists, all must still hold as an article of faith that intestinal worms are harmless. At any rate during the latter part of the 18th and the earlier years of the 19th century, studies of the helminth parasites were confined chiefly to description and classification. A new and vital interest in their biological characteristics developed with the epoch-making researches of Steenstrup, Küchenmeister and Leuckart, all published between 1837 and 1856. Steenstrup demonstrated, using certain intestinal worms as examples, that there exist animal species in which the descendants return to the original adult form only after two or three intervening generations of creatures which in no wise resemble their parents. Küchenmeister and Leuckart established the existence of intermediary hosts for the cestodes. Such startling discoveries concentrated the interest of parasitologists on the problem of working out the life cycle of the various helminths. Raspail's " Natural History of Health and Disease " (1843), in which the importance of parasites in the causation of disease was strongly advocated, was granted scant attention at that epoch. It might have been expected that when Pasteur established the pathogenicity of bacteria there would have been created by the force of analogy a keener interest in the possible etiologic importance of all other parasites. Such an interest, however, was long delayed and when awakened it was directed not towards the worms but towards the protozoa in amebic dysentery and in malaria and later towards the part played by insects in the transmission of disease. The tremendous subsequent expansion of parasitology has firmly established the importance of this category of living creatures in human pathology. Helminthology has benefited from this reawakening but perhaps to a lesser extent than other subdivisions of parasitology. " New fields and pastures new " attracted the investigators and there has been comparative neglect of the worms, especially of most of the worms whose habitat in the adult stage is the human intestine. There are noteworthy exceptions, such as the extensive studies of hookworm infestation and of *Diphyllobothrium latum* anemia; but on the whole there has been least advance in the oldest field of human parasitology.

Perhaps the preoccupation with the descriptive anatomy, the classification and the details of the life cycle of these worms, which is so manifest in our textbooks, is one reason for the lack of development of detailed knowledge concerning their effect on the host. If so, one may view as encouraging the recent researches aimed at disclosing the physiologic processes of the helminths. Such studies are likely to open new vistas as to the nature of their pathogenicity.

McCoy [1] has recently published an interesting review of the work bearing on this aspect of helminthology. From his paper a few examples may be quoted of the significant results being obtained.

[1] McCoy, O. R.: Physiology of the helminth parasites, Phys. Rev., 1935, xv, 221–240.

Respiration and Metabolism: The metabolism of the three main groups of helminth parasites in the parasitic stage, under the practically anaerobic conditions of the intestines, is probably anaerobic. Energy production seems to be derived from the breakdown (fermentative?) of glycogen into carbon dioxide and fatty acids. The nature of these fatty acids varies to some extent with the species of worm; lower volatile acids and higher non-volatile acids have been identified. The production of valeric acid is most frequently mentioned. In the free living period outside the body, metabolic processes in the worm are undoubtedly aerobic.

Nutrition: "Tapeworms lack a mouth and digestive tract and must absorb all their food through the surface of their body. This presumably is composed of substances already digested in the intestine and ready for absorption by the host, and probably consists mainly of sugars. Certain other groups of helminths . . . even though they possess an intestinal tract, apparently subsist on readily absorbed substances rather than on formed substances which would require digestion. Other helminths with digestive tracts (Trematoda and Nematoda), however, have frequently been observed to contain blood corpuscles and other host tissue cells.

"It has been noticed that many helminths which are either wholly or partially embedded in a host tissue cause a necrosis and liquefaction of the tissue in their immediate neighborhood. . . . In certain species of intestinal nematodes Hoeppli interprets the liquefaction of the mucosa around the anterior end of the worm as a form of extra-intestinal digestion in which the tissue is digested by a secretion produced by the parasite. The liquefied tissue then serves as nourishment for the worm.

"Certain intestinal nematodes belonging to the group Strongyloidea are well known blood-suckers and apparently subsist mainly on the blood of their host. The hookworm, which is the best-known example of this group, also ingests portions of intestinal mucosa detached by means of the teeth which arm the buccal cavity. Wells (1931) has recently made an interesting study of the blood sucking activities of the dog hookworm, *Ancylostoma caninum*. He operated on infected dogs under anesthesia, opened a loop of intestine without injuring the blood supply, and was able to observe directly the behavior of the worms on the intestinal mucosa. Under optimum conditions the muscular esophagus of the worms made very rapid sucking movements, sometimes at a rate as high as 120 to 250 pulsations per minute. The sucking of blood went on almost continuously, and persisted even after the posterior part of the worm had been cut off. For the most part the red blood cells passed through the intestine of the hookworm unharmed. By counting the number of corpuscles and measuring the size of the drops ejected through the anus, Wells estimated that on the average one worm would take up as much as 0.84 c.c. of the host's blood per 24 hours."

Growth: There is frequent rigid restriction of parasites to certain species of hosts. The factors which determine this are not at all under-

stood. Worms are not sensitive to wide variations in environmental factors such as hydrogen-ion concentration, oxygen tension, temperature, etc. McCoy has shown that when sterile trichina larvae were introduced into the amniotic sac of rat embryos, a certain proportion were able to develop normally to the adult stage. "These experiments at least show that certain of the factors such as digestive enzymes, bacteria or their products, which are present in the normal intestinal environment, are not necessary for the development of the worms."

Reproduction: In the parasitic stage the helminths guard the perpetuation of their complicated life cycle by various devices. Of these the production of an enormous number of eggs and the occurrence of hermaphroditism and self-fertilization are the most obvious. Little is known of the metabolic processes involved in this massive egg production. It is of interest that if the immunity of the host is raised by repeated reinfections the egg production of the surviving worms in the immune host will be greatly inhibited.

Secretions: Evidence has accumulated that intestinal helminths produce a powerful anti-tryptic enzyme which may not only serve to protect the tissues of the parasite from the digestive juices of the host but may also, if the worms are abundant, reduce tryptic intestinal digestion.

The secretion of anti-coagulins by members of the family Strongyloidae has been known for some time. The substance appears to be related physiologically to hirudin and snake venom.

Worm tissue has been shown to possess rather weak hemolytic qualities but there is no evidence of the secretion of hemolysins. Extracts of worms are often toxic to experimental animals in the sense that when these extracts are injected disturbances of respiration, blood pressure, etc., ensue. However, there is no sound evidence of the formation of true exotoxins. It seems more likely that such "toxic" action as exists is due to the liberation of endotoxins from the bodies of dead worms. "The fact that more or less specific antibodies are developed by the host during helminthic infections has been used as an argument to support the view that worm 'toxins' may be absorbed by the host."

It seems likely that the further development of our knowledge of the physiology of intestinal helminths will furnish many leads for renewed investigations of their pathogenicity.

REVIEWS

Illustrative Electrocardiography. By the late JOSEPH H. BAINTON, M.D., formerly Attending Physician and Chief of the Cardiac Clinic, Morrisania City Hospital, New York, and Consulting Physician, St. John's Long Island City Hospital; and JULIUS BURSTEIN, M.D., Associate Electrocardiographer, Morrisania City Hospital, and Cardiologist to St. Elizabeth Hospital, New York. D. Appleton-Century Co., New York. 1935. Price, $5.00.

This is an atlas which contains examples of normal electrocardiograms and almost all of the various types of abnormal electrocardiograms. The material presented has been selected from a collection of more than 7500 curves, and it appears to be well chosen. Most of the records are good technically. The records are plainly marked to indicate the various deflections and the particular points which they illustrate. Each record is briefly described on the opposite page. The volume contains some interesting and unusual records; the curve of an infant of two days with dextrocardia is of special interest. The work is thoroughly up-to-date, containing brief discussions of coronary occlusion and Lead IV. The interpretations follow well established practice for the most part, although exception must be taken to some of them, particularly bundle branch block in the presence of complete atrio-ventricular block, and wandering, or shifting pacemaker. The chief criticism, however, concerns the brevity of the work. A presentation of the evidence upon which the various interpretations rest would materially enhance the value of the book, especially for the beginner in electrocardiography who needs more ground work than this volume offers.

P. S. B.

Osteomyelitis. By ABRAHAM O. WILENSKY, M.D. 454 pages; 16 × 24 cm. The Macmillan Company, New York. 1934. Price, $9.00.

The author has made an extensive review of the literature of osteomyelitis and presents this mass of information in an interesting manner. Moreover, he discusses the subject with a background of extensive personal experience and presents his own conclusions. In addition to the discussion of etiology, of the clinical aspects of the disease, and of therapy, there is an excellent historical summary in the introduction, and a chapter upon the anatomy of bone.

The "watchful waiting" principle of treatment is advocated in the majority of acute cases which do not show abscess pockets. It is of interest to internists to know that there is a general tendency in recent times to subscribe to this program. The exact time when to cast this policy aside is the crucial test of the surgeon's judgment and may be the critical turning point for the patient. Among surgical methods, the author prefers that of Orr which is certainly the least complicated, but has the disadvantage of producing an unpleasant odor which has almost as unfavorable a psychologic effect as the maggot treatment.

The author's rejection of the maggot treatment is based chiefly on negative facts. Though its satisfactory employment does require an exacting technic and the service of a trained staff, the maggot treatment in stubborn cases has produced results when other methods have failed. It can not be dismissed.

Likewise the author has not given all the space to the use of physical therapy, and particularly ultra-violet light, that this subject deserves. Used intelligently, these methods constitute a valuable adjunct in the therapy of bone disease.

To all those interested in this serious and unfortunately frequent form of infection, this book will serve as a valuable reference volume.

A. V.

Allergy and Applied Immunology. By WARREN T. VAUGHN. Second Edition. 420 pages; 15.5 × 23.5 cm. C. V. Mosby Co., St. Louis. 1934. Price, $5.00.

The author in this volume has set himself the task of presenting a rather comprehensive, even though brief, view of the field of allergy in a manner designed to provide, "a handbook for the intelligent layman."

After a general consideration of the subject of allergy he discusses, in separate sections: allergens, diagnosis, therapy, prognosis, the manifestations of allergy and applied immunology.

Certain impressions are derived from the volume as a whole. First, one feels that a patient must be of a rather high order of intelligence to completely assimilate the material presented in spite of Dr. Vaughn's obvious intent to simplify the subject. Unfortunately, this will probably apply to any similar attempt not because of any short-coming upon the part of the author, but rather, due to the inherent complexity of the subject under discussion. A further impression gained by the reader is that the author of this volume not only knows the subject matter thoroughly but that he possesses the incalculable advantage of a smooth, clear style that immeasurably increases the "readability" of the book.

The approach to the subject of allergy is particularly happy in its gradual and clear development in the mind of the reader of a background of information that renders the following chapters intelligible. One may well criticize the detailed presentation of the theory of protein poisoning, elaborated by the elder Vaughn as an explanation of the phenomena of hypersensitivity, as being too dogmatic, in spite of the warning preceding it that it is simply used as a means of understanding the conditions later described. There can be no criticism, however, of the author's device, designated allergic equilibrium, which is used by him to explain the interplay of the multiplicity of factors governing the allergic reactions as they occur clinically and experimentally.

Section two, devoted to a consideration of the allergens, is splendid, covering this broad field briefly but comprehensively and written in a manner that is surprisingly interesting and is calculated to hold the attention of the lay reader.

Space prevents consideration of each of the sections mentioned above except to say that they are given in an entirely adequate manner. There is an interesting discussion of the effect of biologic grouping upon the production of symptoms. On the whole, however, the reviewer feels that the subject of diet in allergy has been better handled elsewhere.

In summary, one may say that while the book, in parts at least, is probably beyond the capacity of the average patient, it is excellent in itself and a valuable contribution to the literature of allergy.

H. M. B.

Manual of Physical and Clinical Diagnosis. By OTTO SEIFERT and FRIEDRICH MUELLER; translated by E. COWLES ANDRUS, M.D. xi + 561 pages; 13 × 19.5 cm. J. B. Lippincott Company, Philadelphia. 1934. Price, $6.00.

Dr. E. Cowles Andrus of the Johns Hopkins Medical School has made a translation of the thirty-first edition of Seifert and Mueller's well-known manual of physical and clinical diagnosis. It seems likely that this small volume will now attain some of the popularity in this country that it has long enjoyed abroad. It presents in clear and succinct fashion those methods of examination and such tabulated data as are most needed by the physician in practice. It is astonishing how much valuable information can be condensed in a small volume. In the opinion of the reviewer there is no better manual of this type available. The type is not too small; the cuts are well chosen; the binding is attractive. Also, the price is reasonable.

T. C. W.

The Practice of Dietetics. By L. HARRY NEWBURGH, M.D., and FRANCES MACKINNON, A.B. 264 pages; 22 × 15 cm. The MacMillan Company, New York. 1934. Price, $4.00.

This handy-sized volume will be stimulating and helpful reading to the average internist. Part I, "The material needs of the organism," is full of interesting information, as well as both destructive criticism and constructive ideas. It is freshly written and attempts to confine itself to facts. The citation of the actual experimental basis for many of our dietetic notions adds to the interest. When the reader pushes on into Parts II and III, on the selection of food and on therapy by means of diet, he realizes that the author is not attempting to furnish him with directions and diet lists for all known diseases but rather to lay down principles as to the types of diseases in which dietetic treatment is especially important and to instil sound methods of practice. It is a book for students, therefore, be they undergraduates or graduates, and not a helpful quick reference volume for the practitioner.

The author seems to be at one with many other recent students of obesity in going out of his way to misstate the essential problem in this condition. He feels that there is no endogenous factor in obesity and believes this is shown by proving at length (elsewhere) that if the energy intake is less than the expenditure all patients will lose weight. It seems an idle triumph to revindicate the law of the conservation of energy: and it leaves the essential problem untouched.

The chapter on the treatment of diabetes and that on renal disease (by F. H. Lashmet) are clear and interesting statements of the authors' methods in dealing with these two major problems.

M. C. P.

COLLEGE NEWS NOTES

Gifts to the College Library

Acknowledgment is made of the receipt of the following donations to the College Library of publications by members:

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Dr. Bert F. Keltz (Associate), Oklahoma City, Okla.—2 reprints.

Sectional Meetings of College Members

During meetings of the Board of Governors in connection with the Philadelphia Annual Session of the College, several Governors reported that they had conducted sectional gatherings of College members of their territories.

Kentucky

On January 19, 1935, the Kentucky members of the College met in Louisville. Dr. John Walker Moore and his associates, together with Dr. J. Murray Kinsman and Dr. John J. Moren, conducted a very interesting clinic at the Louisville City Hospital, which was followed by dinner at the Pendennis Club. The whole affair was informal and was so enjoyed that it was voted unanimously to meet in this way at least once each year. Twenty-seven out of a total of 43 Fellows and Associates were present. The next meeting will be held in Lexington at a time to be chosen later. The meeting was arranged through Dr. Ernest B. Bradley, former Governor of the College for Kentucky.

District of Columbia

Fellows and Associates of the College from the District of Columbia attended a local clinical assembly held at the Gallinger Municipal Hospital on Tuesday, April 16. There were four clinics of one-half hour each as follows: cardiology clinic by Dr. Thomas S. Lee; medical clinic by Dr. Walter A. Bloedorn; tuberculosis clinic by Dr. Charles P. Cake; neurological clinic by Dr. Walter Freeman. Free discussion was encouraged. Dr. William Gerry Morgan, Secretary-General of the College, gave a brief address, which was followed by a luncheon tendered by Dr. Bocock, Superintendent of the Hospital. The meeting was arranged through the instrumentality of Dr. Wallace M. Yater, Governor of the College for the District of Columbia.

REGISTRATION STATISTICS, PHILADELPHIA (1935) SESSION, AMERICAN COLLEGE OF PHYSICIANS

	Member Physicians	Guest Physicians	Sr. Med. Students	Visiting Women	Exhibitors	Total
UNITED STATES AND POSSESSIONS:						
Alabama	7			1		8
Arizona	1					1
Arkansas	4	3		2		9
California	18	3		5		26
Colorado	8	1		2		11
Connecticut	24	3		1	3	31
Delaware	6	1				7
District of Columbia	32	5	1			38
Florida	7	3				10
Georgia	8	1				9
Idaho	1					1
Illinois	18	6		6	22	52
Indiana	10	6		2	1	19
Iowa	9	1		4		14
Kansas	7	3				10
Kentucky	18			3	2	23
Louisiana	9	1		2		12
Maine	8	1		3		12
Maryland	27	4	1	5	2	39
Massachusetts	38	10		9	8	65
Michigan	34	5		13	10	62
Minnesota	18	4		5		27
Mississippi	3			1		4
Missouri	13	1		3	2	19
Montana	3					3
Nebraska	15	1		3		19
New Hampshire	2					2
New Jersey	49	12		5	25	91
New York	123	28		25	51	227
North Carolina	32	6		8		46
North Dakota	2					2
Ohio	53	14		14	8	89
Oklahoma	9			3		12
Oregon	3					3
Pennsylvania	194	606	344	43	93	1,280
Rhode Island	8			3		11
South Carolina	3					3
South Dakota	1					1
Tennessee	7	1		2		10
Texas	14	1		4		19
Utah	2			1		3
Vermont	1	1				2
Virginia	28	3		4		35
Washington	3			2		5
West Virginia	8	1		2		11
Wisconsin	9			3	3	15
Wyoming	2					2
Puerto Rico	2					2
Philippine Islands	1					1
CANADA						
Alberta	1			1		2
Ontario	11	6		2		19
Quebec	9	4		2	1	16
OTHER COUNTRIES						
Brazil		1				1
China		1				1
Cuba		1		1		2
TOTAL	923	749	346	195	231	2,444

At the Eleventh Annual Meeting of the American Association of the History of Medicine held in Atlantic City, May 6, Dr. William S. Middleton (Fellow), Madison, Wis., was elected President; Dr. Walter C. Alvarez (Fellow), Rochester, Minn., was elected Vice-President; Dr. E. J. G. Beardsley (Fellow), Philadelphia, Pa., was elected Secretary, and Dr. Carl V. Weller (Fellow), Ann Arbor, Mich., was elected a member of the Council.

During the meeting, Dr. Harlow Brooks (Fellow), New York City, presented an historical paper entitled "A Navajo Medicine Sing," and Dr. Walter C. Alvarez (Fellow), Rochester, Minn., presented a paper entitled "Folklore a Physician Should Know."

Dr. Howard T. Karsner (Fellow), Professor of Pathology in the Western Reserve University, Cleveland, Ohio, was recently elected to membership in the *Association Française pour l'Étude du Cancer*, the French Association for the Study of Cancer.

The 1935 Graduate Fortnight of the New York Academy of Medicine will be held October 21 to November 2, and will be devoted to a consideration of diseases of the respiratory tract. Eighteen important hospitals will present coördinated afternoon clinics and clinical demonstrations. At the evening meetings, prominent clinicians from various parts of the country will discuss various aspects of the general subject. Among Fellows of the College who will be speakers at the evening meetings are: Drs. James Alex. Miller, Jonathan C. Meakins, J. Burns Amberson, George Blumer, Henry Chickering, Maximilian A. Ramirez and David Riesman.

Under the Presidency of Dr. Samuel E. Munson (Fellow), Springfield, Ill., the District Medical Society of Central Illinois held its Sixty-First Annual Meeting at Springfield on April 17. Among others who presented papers were Dr. Walter L. Bierring (Fellow), President of the American Medical Association, and Dr. Andrew C. Ivy (Fellow), Head of the Department of Physiology and Pharmacology of Northwestern University Medical School.

The Sixth Annual Staff Demonstration Week of the Hackensack (Hackensack, N. J.) Hospital was conducted April 15 to 19, under the direction of its Medical Board, on which Dr. Herman Trossbach (Fellow) is Director of Medicine and Dr. Richard E. Knapp (Fellow) is Director of X-Ray. Dr. Trossbach presented a demonstration on artificial pneumothorax in the treatment of lobar pneumonia, and Dr. Richard E. Knapp discussed the x-ray interpretations. Dr. George M. Levitas (Fellow) contributed to the pediatric program a paper on "Prevention of 'Physiological' Weight Loss in the New Born."

Dr. Henry Wallace (Fellow), New York City, was the guest of honor and speaker at the Annual Alumni Luncheon of the Long Island College Hospital, Brooklyn, recently. His topic was "Memoirs of an Old Timer." Dr. Wallace was a member of the class of 1890. He became a Fellow of the American College of Physicians in 1920.

The Mississippi State Board of Health, through its Executive Officer, Dr. Felix J. Underwood (Fellow), has engaged in a program of radio talks for the purpose of disseminating information on preventive medicine and public health policies to the citizens of that State.

Dr. Ralph H. Kuhns (Fellow), Chicago, addressed the Miami Valley Hospital Society at Dayton, Ohio, May 3, on "Fever Therapy for Dementia Paralytica."

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